R0142B-REG B1

(19) Europäis h Pat ntamt
European Patent Office
Offic européen d s brev t

(11) EP 1 055 668 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
29.11.2000 Bulletin 2000/48

(51) Int Cl.[7]: C07D 211/26, C07D 401/04, C07D 413/04, A61K 31/454, A61P 17/04

(21) Application number: 00304227.2

(22) Date of filing: 18.05.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 28.05.1999 GB 9912413

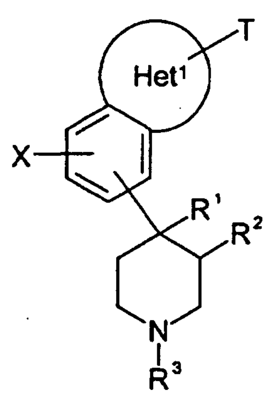
(71) Applicants:
- PFIZER INC.
New York, N.Y. 10017-5755 (US)
Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
- Pfizer Limited
Sandwich Kent CT13 9NJ (GB)
Designated Contracting States:
GB

(72) Inventors:
- Armer, Richard Edward, Akzo Nobel Newhouse, Scotland ML1 5SH (GB)
- Bronk, Brian Scott, Pfizer Inc. Groton, Connecticut 06340 (US)
- Gibson, Stephen Paul, Pfizer Central Research Sandwich, Kent CT13 9NJ (GB)
- Roberts, Lee Richard, Pfizer Central Research Sandwich, Kent CT13 9NJ (GB)
- Tommasini, Ivan, Pfizer Central Research Sandwich, Kent CT13 9NJ (GB)
- Verrier, Kimberley, Pfizer Central Research Sandwich, Kent CT13 9NJ (GB)

(74) Representative: Eddowes, Simon et al
Urquhart-Dykes & Lord,
30 Welbeck Street
London, W1M 7PG (GB)

(54) **New 4-arylpiperidine derivatives for the treatment of pruritus**

(57) There is provided a compound of formula I,



I

wherein Het^1, T, X, R^1, R^2 and R^3 have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opiate receptors, such as pruritus.

EP 1 055 668 A1

Description

[0001] This inv ntion relates to pharmaceutically useful compounds, in particular compounds that bind to opiat r ceptors (.g. mu, kappa and delta opioid receptors).

[0002] Compounds that bind to such receptors are likely to be useful in the treatment of diseases m diated by opiate receptors, for example irritable bowel syndrome; constipation; nausea; vomiting; and pruritic dermatoses, such as allergic dermatitis and atopy in animals and humans. Compounds that bind to opiate receptors have also been indicated in the treatment of eating disorders, opiate overdoses, depression, smoking and alcohol addiction, sexual dysfunction, shock, stroke, spinal damage and head trauma.

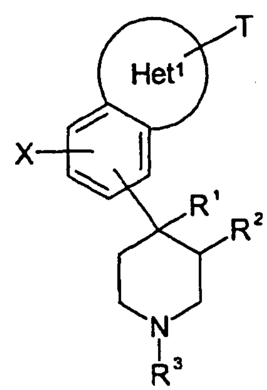
[0003] There is a particular need for an improved treatment of itching. Itching, or pruritus, is a common dermatological symptom that can give rise to considerable distress in both humans and animals. Pruritus is often associated with inflammatory skin diseases which may be caused by hypersensitivity reactions, including reactions to insect bites, such as flea bites, and to environmental allergens, such as house dust mite or pollen; by bacterial and fungal infections of the skin; or by ectoparasite infections.

[0004] Existing treatments that have been employed in the treatment of pruritus include the use of corticosteroids and antihistamines. However, both of these treatments are known to have undesirable side effects. Other therapies that have been employed include the use of essential fatty acid dietary supplements, though these have the disadvantages of being slow to act, and of offering only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed, but with limited success.

[0005] Thus, there is a continuing need for alternative and/or improved treatments of pruritus.

[0006] Certain 4-arylpiperidine-based compounds are disclosed in *inter alia* European patent applications EP 287339, EP 506468, EP 506478 and J. *Med. Chem.* **1993**, 36, 2833-2850 as opioid antagonists. In addition, International Patent Application WO 95/15327 discloses azabicycloalkane derivatives useful as neuroleptic agents.

[0007] According to the invention there is provided compounds of formula I:



I

wherein Het^1 represents a 5-, 6- or 7-membered heterocyclic ring containing at least one nitrogen atom, and optionally one or more heteroatoms selected from oxygen or sulfur, and which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character; T represents one or more optional substituents selected from H, halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which latter three groups are optionally substituted by one or more halo atoms), aryl (C_{1-6})alkyl (the aryl part of which is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), -N(R^{4a})(R^5), -N(R^{4b})S(O)$_m$$R^6$, -N($R^{4c}$)C(O)$R^{7a}$ and -N(R^{4d})C(O)OR^{7b}, provided that when Het^1 contains less than three C-atoms (i.e. where the only two C-atoms are those provided by the fused benzene ring) and at least one heteroatom selected from oxygen and sulfur, then T does not represent halo or C_{1-6} alkoxy (which latter group is optionally substituted by one or more halo atoms);

R^{4a} to R^{4d} and R^5 independently represent H, C_{1-6} alkyl (which latter group is optionally substituted by one or more halo atoms), or R^{4a} and R^5, together with the nitrogen atom to which they are attached, form a 4- to 6-membered heterocyclic ring (which ring is optionally substituted by one or more substituents s lect d from C_{1-4} alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo);

R^6 represents C_{1-6} alkyl or aryl, which two groups are ptionally substituted by one or m r substitu nts selected from halo, C_{1-4} alkyl or nitro;

R^{7a} and R^{7b} independently r present C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, aryl (which four groups are optionally substituted by on or more substitu nts selected from halo, C_{1-4} alkyl or nitro), or R^{7a} represents H;
m is 0, 1 or 2;
R^1 and R^2 are each independently H or C_{1-4} alkyl;
R^3 represents aryl (optionally substitut d by one or more substituents sel cted from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter thre groups are optionally substituted by on or mor halo atoms) and $-N(R^{8a})(R^{8b})$), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{8c}, $S(O)_nR^{8d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{9a})S(O)_2R^{10}$, Het^2, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{9b})(R^{9c})$;
n is 0, 1 or 2;
W represents a single bond, C(O) or $S(O)_p$;
A^1 represents a single bond or C_{1-10} alkylene;
provided that when both W and A^1 represent single bonds, then the group $-N(R^{9b})(R^{9c})$ is not directly attached to an unsaturated carbon atom;
p is 0, 1 or 2;
R^{8a} to R^{8d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het^3;
provided that R^{8d} does not represent H when n represents 1 or 2;
R^{9a} to R^{9c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^4, or R^{9b} and R^{9c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O, S and/or an $N(R^{11})$ group and is optionally substituted by one or more C_{1-4} alkyl groups;
R^{10} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, nitro, amino or halo;
R^{11} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, A^2-(C_{3-8} cycloalkyl) or A^2-aryl;
A^2 represents C_{1-6} alkylene;
Het^2, Het^3 and Het^4 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);
X represents one or two optional substituents on the benzene ring, which substituents are selected from halo, C_{1-4} alkyl, C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);
or pharmaceutically, or veterinarily, acceptable derivatives thereof;
which compounds are referred to together hereinafter as "the compounds of the invention."

[0008] In the definitions used herein, alkyl, alkylene, alkoxy, alkoxy carbonyl, alkanoyl, alkanoyloxy, alkenyl, alkynyl and the alkyl parts of alkylphenyl and aryl alkoxy groups may, when there is a sufficient number of carbon atoms, be straight or branched-chain and/or optionally interrupted by one or more oxygen and/or sulfur atom(s). The term halo includes fluoro, chloro, bromo or iodo. The term "aryl" includes optionally substituted phenyl, naphthyl and the like, and "aryloxy" includes optionally substituted phenoxy and naphthyloxy and the like. Unless otherwise specified, aryl and aryloxy groups are optionally substituted by one or more (e.g. one to three) substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkoxy carbonyl and C_{1-5} alkanoyl (which latter four groups are optionally substituted by one or more halo atoms).

[0009] The heterocyclic rings that Het^2, Het^3 and Het^4 represent and that $N(R^{4a})(R^5)$ may represent, may be fully saturated, partially unsaturated and/or wholly or partially aromatic in character. Specific rings that may be mentioned include: for Het^2, dioxane, dioxolane, morpholine, piperidine, perhydroazepine, tetrahydrofuran, tetrahydropyran or tetrazole.

[0010] For the avoidance of doubt, when heterocyclic groups (i.e. Het^2, Het^3, Het^4 and some definitions of $N(R^{4a})(R^5)$) are at least part-saturated, possible points of substitution include the atom (e.g. the carbon atom) at the point of attachment of the heterocyclic group to the rest of the mol cule. Het (Het^2, Het^3 and Het^4) groups may also be attach d to the rest of th molecule *via* a h teroatom.

[0011] The piperidine moiety in compounds of formula I may b in N-oxidised form. Sulfur atoms that may interrupt

(e.g. alkyl) substituents in compounds of formula I may be present in oxidised form (e.g. as sulfoxides or sulfones). All heterocyclic groups (i.e. Het^1, Het^2, Het^3, Het^4 and some definitions of N(R^4)(R^5)) may also be in N- or S-oxidiz d forms.

[0012] The term "pharmac utically, or veterinarily, acc ptable derivatives" includes non-toxic salts. Salts which may be mentioned include: acid addition salts, for example, salts f rmed with sulfuric, hydrochloric, hydr bromic, phosphoric, hydroiodic, sulfamic, organo-sulfonic, citric, carboxylic (e.g. acetic, benzoic, etc.), maleic, malic, succinic, tartaric, cinnamic, ascorbic and related acids; base addition salts; salts formed with bases, for example, the sodium, potassium and C_{1-4} alkyl ammonium salts.

[0013] The compounds of the invention may also be in the form of quaternary ammonium salts, e.g. at the piperidine moiety, which salts may be formed by reaction with a variety of alkylating agents, such as an alkyl halide or an ester of sulfuric, or an aromatic sulfonic, acid.

[0014] The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formula I are included within the scope of the invention.

[0015] The compounds of the invention contain one or more asymmetric centres and thus they can exist as enantiomers and diastereomers. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techniques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. The invention includes the use of both the separated individual isomers as well as mixtures of isomers.

[0016] Also included within the scope of the invention are radiolabelled derivatives of compounds of formula I which are suitable for biological studies.

[0017] Preferred compounds of the invention include those wherein:

Het^1 is fused at the 3,4-position on the benzene ring relative to the piperidine ring;

R^1 represents C_{1-2} alkyl;

R^2 represents H or C_{1-2} alkyl;

R^3 represents saturated C_{1-10} (e.g. C_{1-8}) alkyl, optionally interrupted by oxygen and/or optionally substituted by one or more substituents selected from OR^{8c}, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{9a})S(O)_2R^{10}$, Het^2, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN, CH_2CN, $CONH_2$ and CF_3), and/or $-W-A^1-N(R^{9b})(R^{9c})$;

R^{8c} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl or C_{1-4} alkylphenyl (which latter two groups are optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN, CH_2CN, $CONH_2$ and CF_3);

R^{9a} to R^{9c} each independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter two groups are optionally substituted by or one or more substituents selected from C_{1-2} alkyl, C_{1-2} alkoxy, OH or halo);

R^{10} represents C_{1-4} alkyl or aryl, which two groups are optionally substituted by or one or more substituents selected from C_{1-2} alkyl, C_{1-2} alkoxy, nitro or halo;

W represents C(O) or $S(O)_2$;

A^1 represents a single bond or C_{1-4} alkylene;

T represents H, OH, C_{1-6} alkyl (optionally substituted with one or more halo atoms), C_{1-4} alkoxy, C_{4-6} cycloalkyl, aryl (C_{1-3})alkyl, $-NH(R^5)$ or $-N(H)S(O)_2R^6$;

R^5 represents H or C_{1-2} alkyl;

R^6 represents C_{1-2} alkyl.

[0018] More preferred compounds of the invention include those wherein:

Het^1 represents a 5- or 6-membered heterocyclic ring, optionally containing an NH group;

R^1 represents methyl;

R^2 represents H or methyl;

R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from OR^{8c}, CN, halo and phenyl (which latter group is optionally substituted by one or more C_{1-4} alkyl groups);

R^{8c} represents H, C_{1-4} alkyl, phenyl or C_{1-4} alkylphenyl (which latter two groups are optionally substituted by one or more C_{1-4} alkyl groups);

T represents H, NH_2, C_{4-6} cycloalkyl or C_{1-6} alkyl (which latter group is optionally substituted by one or more halo atoms);

X represents halo, particularly fluoro.

[0019] Still further preferred compounds of the inv ntion include those wherein:

Het^1, tog ther with the benzene ring to which it is fused, r pres nts an aromatic heterocycl , particularly a benzimidazole, benzotriaz le, benzoxadiazole, benzoxazole, benzothiazole, cinnoline, indole, isoquinoline, phthalazine,

quinazoline, quinoline or quinoxaline group;
T represents H, CH_3, CHF_2, CF_3, ethyl, isopropyl, C_{4-5} cycloalkyl r NH_2;
R^1 and R^2 both repres nt methyl groups in the mutually *trans* configuration;
R^3 repres nts saturated C_{1-7} alkyl, optionally substituted by on or mor substitu nts sel cted from OR^{8c} and ph nyl, (which latter group is optionally substituted by one or more C_{1-2} alkyl groups);
R^{8c} represents C_{2-4} alkyl, phenyl or C_{1-2} alkylphenyl.

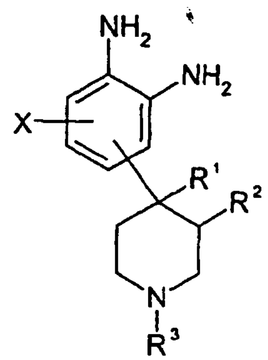
[0020] Particularly preferred compounds of the invention include those wherein:
Het^1, together with the benzene ring to which it is fused, represents a benzimidazole group;
T represents H, CHF_2 or CF_3.

[0021] Preferred compounds of the invention include the compounds of the Examples described hereinafter.

[0022] According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

[0023] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

[0024] 1. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which three groups are optionally substituted by one or more halo atoms) or aryl(C_{1-6})alkyl (the aryl part of which is optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy, which latter two groups are optionally substituted by one or more halo atoms), may be prepared by reaction of a corresponding compound of formula II,



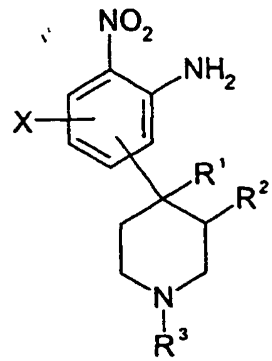
II

wherein R^1, R^2, R^3 and X are as hereinbefore defined, with a compound of formula III,

$$T^a\text{-}C(OR^{12})_3 \qquad \text{III,}$$

wherein T^a represents H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which latter three groups are optionally substituted by one or more halo atoms) or aryl(C_{1-6})alkyl (the aryl group of which is optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy, which latter two groups are optionally substituted by one or more halo atoms) and R^{12} represents C_{1-2} alkyl, for example at between room and reflux temperature in the presence of a suitable solvent and/or acidic catalyst (e.g. acetic acid).

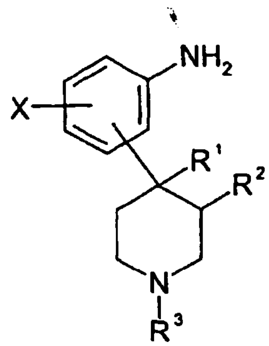
[0025] Compounds of formula II may be prepared by reduction of a corresponding nitroaniline of formula IV,



IV

wherein R^1, R^2, R^3 and X are as hereinbefore defined, for example by hydrogenation under standard catalytic conditions, or in the presence of a suitable reducing agent (e.g. finely divided metallic iron combined with calcium chloride) and an appropriate solvent (e.g. water or a water/alcohol mixture).

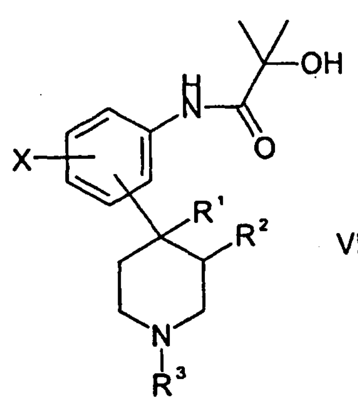
[0026] Compounds of formula IV may be prepared by nitration of a corresponding aniline of formula V,



V

wherein R^1, R^2, R^3 and X are as hereinbefore defined, under conditions known to those in the art, for example by reaction with a suitable nitronium salt (e.g. nitronium tetrafluoroborate) in the presence of an appropriate solvent (e.g. acetonitrile).

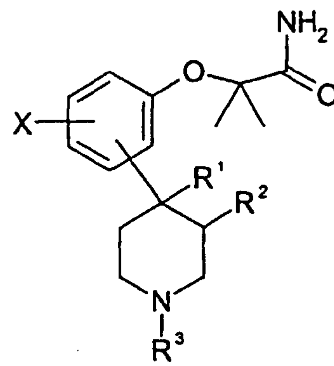
[0027] Compounds of formula V may be prepared by hydrolysis of a corresponding compound of formula VI,



VI

wher in R^1, R^2, R^3 and X are as her inbefore defined, und r conditions known to those skilled in the art, for xample by r action at between room and reflux temperatur with a suitable str ng acid (.g. HCl) and (optionally) an appropriate co-solvent (e.g. dioxan).

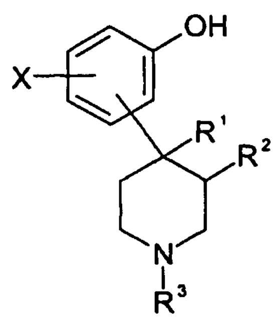
[0028] Compounds f formula VI may be pr pared by r arrangement of a corr sponding comp und of formula VII,



VII

wherein R^1, R^2, R^3 and X are as hereinbefore defined, for example at between 25 and 200°C in the presence of a suitable strong base (e.g. sodium hydride) and an appropriate solvent (e.g. 1-methyl-2-pyrrolidinone or *N,N*-dimethylformamide).

[0029] Compounds of formula VII may be prepared by reaction of a corresponding compound of formula VIII,



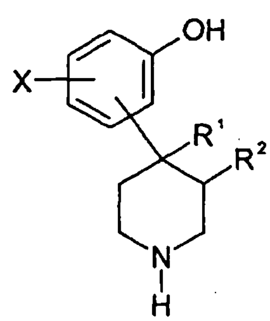
VIII

wherein R^1, R^2, R^3 and X are as hereinbefore defined, with a compound of formula IX,

$$L^1\text{-}C(CH_3)_2C(O)NH_2 \qquad \text{IX}$$

wherein L^1 is a suitable leaving group (e.g. halo, arene sulfonate, alkane sulfonate or perfluoroalkane sulfonate), for example at between room and reflux temperature in the presence of a suitable base (e.g. caesium carbonate in combination with sodium hydride) and an appropriate solvent (e.g. dioxan).

[0030] Compounds of formula VIII may be prepared by reaction of a corresponding compound of formula X,



X

wherein R^1, R^2 and X are as hereinbefore defined, with a compound of formula XI,

$$R^3L^1 \qquad \text{XI}$$

wherein R^3 and L^1 are as hereinbefore defined, for example under conditions known to those skilled in the art, which include, for example, alkylation at between room temperature and reflux temperature in the presence of a reaction-inert organic solvent (e.g. *N,N*-dimethylformamide) and a suitable base (e.g. $NaHCO_3$), and arylation at between room temperature and reflux temperature in the presence of a suitable catalyst system (e.g. tris(dibenzylideneacetone)palladium(0) combined with tri-*o*-tolylphosphine), an appropriate strong base (e.g. sodium *tert*-butoxide) and a reaction-inert solvent (e.g. toluene).

[0031] 2. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by T^a, wherein T^a is as hereinbefore defined provided that it does not represent C_{1-6} alkoxy or C_{1-6} haloalkoxy, may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula XII,

$$T^a\text{-C(O)OH} \qquad \text{XII}$$

or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or an anhydride), wherein T^a is as hereinbefore defined provided that it does not represent C_{1-6} alkoxy or C_{1-6} haloalkoxy, for example at between room temperature and 250°C.

[0032] 3. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by a hydroxy group, may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a suitable derivative of carbonic acid (e.g. urea), for example at between room and reflux temperature in the presence of a suitable solvent (e.g. *N,N*-dimethylformamide).

[0033] 4. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, substituted in the 2-position by a $N(H)S(O)_2R^6$ group, wherein R^6 is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula XIII,

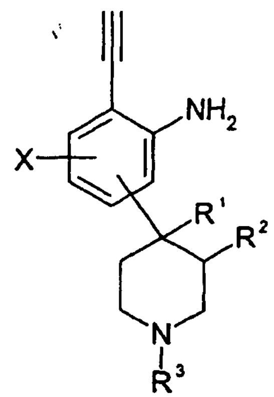
$$(L^2)_2C = NS(O)_2R^6 \qquad \text{XIII}$$

wherein L^2 represents a leaving group (such as halo) and R^6 is as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. toluene).

[0034] 5. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, substituted in the 2-position by an amino group, may be prepared by hydrolysis of a corresponding compound of formula I in which Het^1 represents the 5-membered ring of a benzimidazole substituted in the 2-position by a $N(H)S(O)_2R^6$ group, wherein R^6 is as hereinbefore defined, for example under conditions known to those skilled in the art.

[0035] 6. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzotriazole may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a suitable source of the nitrosonium cation (e.g. sodium nitrite combined with concentrated HCl), for example at between -10°C and room temperature in the presence of a reaction-inert solvent (e.g. a lower alkyl alcohol such as ethanol).

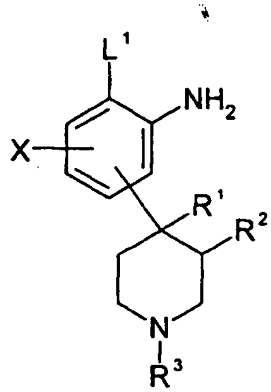
[0036] 7. Compounds of formula I wherein Het^1 represents the 5-membered ring of an indole may be prepared by cyclisation of a corresponding compound of formula XIV,



XIV

wherein R^1, R^2, R^3 and X are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable activator (e.g. copper(I) iodide) and a reaction-inert solvent (e.g. *N,N*-dimethylformamide).

[0037] Compounds of formula XIV may be prepared by reaction of a corresponding compound of formula XV,

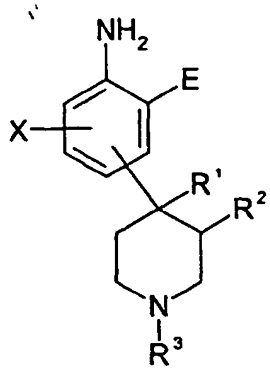


XV

wherein R^1, R^2, R^3, L^1 and X are as hereinbefore defined, with acetylene, for example at between room and reflux temperature in the presence of a suitable catalyst system (e.g. bis(triphenylphosphine)palladium(II) chloride combined with copper(I) iodide) and an appropriate organic base (e.g. triethylamine).

[0038] Compounds of formula XV in which L^1 represents chloro, bromo or iodo may be prepared by reaction of a corresponding compound of formula V, as hereinbefore defined, with a halogen under conditions known to those skilled in the art (e.g. by reaction with a solution of the halogen in acetic acid).

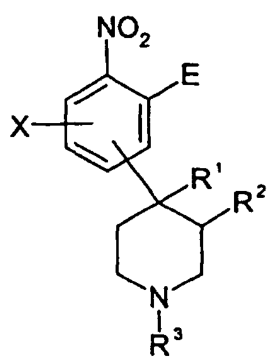
[0039] 8. Compounds of formula I wherein Het^1 represents the 5-membered ring of a benzoxazole or benzothiazole, optionally substituted in the 2-position by T^a, wherein T^a is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XVI,



XVI

wherein E represents OH or SH, and R^1, R^2, R^3 and X are as hereinbefore defined, with a compound of formula III or a compound of formula XII, as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. xylene) and (as appropriate) a suitable catalyst (e.g. pyridinium *para*-toluenesulfonate) or a suitable base (e.g. triethylamine).

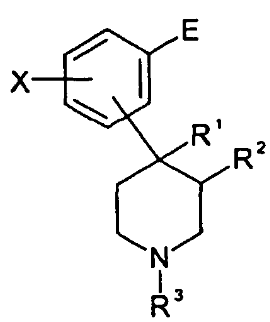
[0040] Compounds of formula XVI may be prepared by reduction of a corresponding compound of formula XVII,



XVII

wherein R^1, R^2, R^3, E and X are as hereinbefore defined, under conditions known to those skilled in the art (e.g. under conditions such as those described hereinbefore for the production of compounds of formula II).

[0041] Compounds of formula XVII may be prepared by nitration of a corresponding compound of formula XVIII,



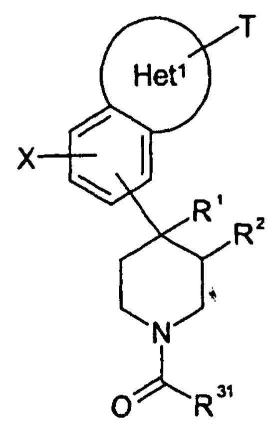
XVIII

wh r in R^1, R^2, R^3, E and X ar as her inbefore defined, for example under nitration conditions known to those skilled in the art (.g. under conditions such as thos described hereinbefore for the production of compounds of formula IV).

[0042] 9. Compounds of formula I wherein Het^1 represents the 5-memb red ring of a benzoxazole or benzothiazole, optionally substituted in th 2-position with an OH group, may b pr pared by reaction of a corresponding compound of formula XVI, as hereinb fore defin d, with a suitable derivative of carbonic acid (.g. 1,1'-carbonyldiimidazole), for

example at between 0°C and reflux temperature in the presence of a reaction-inert solvent (e.g. *N,N*-dimethylformamide).

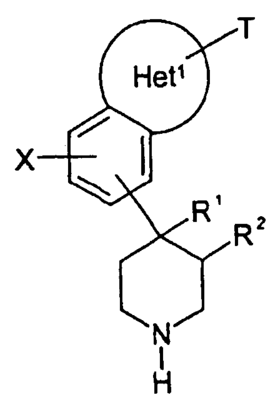
[0043] 10. Compounds of formula I wherein R^3 r presents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^2, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter thre groups ar optionally substituted by one or more halo atoms)), r R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl r C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore in respect to R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^2 is as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula XIX,



XIX

wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^2, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{8c}, $S(O)_nR^{8d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{9a})S(O)_2R^{10}$, Het^2, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{9b})(R^{9c})$, and R^1, R^2, R^{8c}, R^{8d}, R^{9a} to R^{9c}, R^{10}, Het^1, Het^2, n, W, A^1, T and X are as hereinbefore defined, using a suitable reducing agent (e.g. lithium aluminium hydride or a borane derivative), for example as described hereinbefore.

[0044] Compounds of formula XIX may be prepared by reaction of a corresponding compound of formula XX,



XX

wh rein Het^1, R^1, R^2, T and X are as hereinbefore defined with a compound of formula XXI,

$$R^{31}CO_2H \qquad XXI$$

or a suitable (e.g. carboxylic acid) derivativ thereof (.g. an acid halide or anhydride), wherein R^{31} is as hereinbefor defined, using coupling conditions known to those skilled in the art.

[0045] Compounds of formulae XIX and XX may be prepared from appropriate precursors by analogy with methods disclosed herein that describe the formation of a Het^1 group.

[0046] 11. Compounds of formula I may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, under conditions that are known to those skilled in the art, for example as described hereinbefore in respect of the production of compounds of formula VIII.

[0047] 12. Compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31}, wherein R^{31} is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXII,

$$R^{31}CHO \qquad XXII$$

wherein R^{31} is as hereinbefore defined, for example in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride) and an appropriate solvent (e.g. methanol).

[0048] 13. Compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{8d}$, $S(O)_2R^{8d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{9b})(R^{9c})$, $-S(O)-A^1-N(R^{9b})(R^{9c})$, or $-S(O)_2-A^1-N(R^{9b})(R^{9c})$, wherein R^{8d}, R^{9b}, R^{9c} and A^1 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXIII,

$$R^{3a}\text{-}Z \qquad XXIII$$

wherein R^{3a} represents R^3 as hereinbefore defined except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{8d}$, $S(O)_2R^{8d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{9b})(R^{9c})$, $-S(O)-A^1-N(R^{9b})(R^{9c})$, or $-S(O)_2-A^1-N(R^{9b})(R^{9c})$, wherein R^{8d}, R^{9b}, R^{9c} and A^1 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF).

[0049] Compounds of formulae III, IX, X, XI, XII, XIII, XV (in which L^1 does not represent chloro, bromo or iodo), XVIII, XXI, XXII, XXIII and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

[0050] Compounds of formula I, XIX and XX containing other Het^1 rings (in particular, 6- and 7-membered rings) may obtained by analogy with the processes described herein. For example, 7-membered Het^1 rings containing 2 nitrogen atoms may be prepared by analogy with process 2 described hereinbefore. Other Het^1 rings, for example 7-membered Het^1 rings containing 4 nitrogen atoms, may be made by methods known in the art such as those described in Comprehensive Heterocyclic Chemistry II, edited by AR Katritsky, CW Rees and EFV Scriven, 1st Edition, Elsevier Science Ltd. (1996), or by the methods described in The Chemistry of Heterocyclic Compounds, by A Weissberger (John Wiley and Sons), Volumes 5 (1953), 33 (1978) and 50 (1991), the disclosures in which documents are hereby incorporated by reference.

[0051] It will be appreciated by those skilled in the art that the compounds delivered by the aforementioned processes can be further modified by interconverting the substituents on the aromatic moieties to other desired substituents (see, for example, Comprehensive Heterocyclic Chemistry II, edited by AR Katritsky, CW Rees and EFV Scriven, 1st Edition, Elsevier Science Ltd. (1996)). For example, nitro may be reduced to amino, OH may be alkylated to give alkoxy, alkoxy may be hydrolysed to OH, alkenes may be hydrogenated to alkanes, halo may be hydrogenated to H, etc. Substituents on alkyl groups in the above-mentioned compounds may also be introduced, removed and interconverted, using techniques which are well known to those skilled in the art.

[0052] In s me cases it is possibl to introduce further substituents into the compounds of formula I directly. For exampl , chlorination of the phenyl gr up of compounds of formula I, may b performed by reaction with a solution of chlorine in acetic acid.

[0053] The skilled person will also appreciate that these, and other, various standard substituent or functional group interconversions and transformations within certain c mpounds of formula I will provide other compounds of formula I.

[0054] Th compounds of the invention may b isolated from their reaction mixtur s using conventional techniques.

[0055] It will be appreciated by those skilled in the art that, in the course of carrying out the proc sses described above, the functional groups of intermediate compounds may ne d to be protected by protecting groups.

[0056] Functional groups which it is desirable to protect include oxo, OH, amino and carboxylic acid. Suitable protective groups for oxo include acetals, ketals (e.g. ethylene ketals) and dithianes. Suitable protective groups for OH include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protective groups for amino include *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl or ethanoyl. Suitable protective groups for carboxylic acid include C_{1-6} alkyl or benzyl esters. Suitable protective groups for terminal alkynes include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl).

[0057] The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

[0058] Protective groups may be removed in accordance with techniques which are well known to those skilled in the art.

[0059] The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

[0060] Persons skilled in the art will also appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

[0061] It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

[0062] It will be further appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described in 'Design of Prodrugs' by H. Bundgaard, Elsevier, **1985** (the disclosure in which document is hereby incorporated by reference), may be placed on appropriate functionalities, when such functionalities are present within compounds of formula I. For example, biolabile groups may be placed on functional groups of compounds of formula I (e.g. an NH functionality in a Het^1 group), and in the case of 5- or 6-membered Het^1 rings containing NH functionalities, such biolabile derivatives may be preferred.

[0063] All protected and biolabile derivatives, and prodrugs, of compounds of formula I are included within the scope of the invention.

[0064] Pharmaceutically acceptable acid addition salts of the compounds of formula I which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration of by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula I with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

[0065] The above procedures may be adapted as appropriate to the particular reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples provided hereafter to enable all of the compounds of formula I to be prepared.

[0066] The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals including humans. They are therefore indicated as pharmaceuticals and, in particular, for use as animal medicaments.

[0067] According to a further aspect f the invention there is provided the compounds of the invention for use as medicaments, such as pharmaceuticals and animal medicaments.

[0068] By the term "treatment", we include b th therapeutic (curative) or prophylactic treatment.

[0069] In particular, the compounds of the inv ntion have been found to be useful in the treatment of diseases m - diat d *via* opiate receptors, which diseases include irritabl bowel syndrome; constipation; nausea; vomiting; pruritus; and c nditions characteris d by pruritus as a symptom.

[0070] Thus, according to a further aspect of th invention there is provided the use of the compounds f the invention in the manufacture of a medicament for the treatment of a disease mediated *via* an opiat receptor. Ther is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom.

[0071] The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and conditions which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

[0072] Thus, the invention provides a method of treating or preventing a disease mediated *via* an opiate receptor. There is further provided a method of treating irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom in an animal (e.g. a mammal), which comprises administering a therapeutically effective amount of a compound of the invention to an animal in need of such treatment.

[0073] The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

[0074] While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

[0075] The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

[0076] The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

[0077] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

[0078] In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0079] For veterinary use, the compounds of the invention are of particular value for treating pruritus in domestic animals such as cats and dogs and in horses.

[0080] As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

[0081] For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet, capsule and ointment preparations which are formulated in accordance with standard pharmaceutical practice.

[0082] Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of illustration and should not be construed as limiting) include antiparasitics, e.g. fipronil, lufenuron, imidacloprid, avermectins (e.g. abamectin, iv rmectin, doramectin), milb mycins, organophosphates, pyr throids; antihistamines, e.g. chlorpheniramin , trimeprazine, diphenhydramine, doxylamine; antifungals, .g. fluconaz l , ketoconaz le, itraconazole, gris ofulvin, amphotericin B; antibacterials, .g. nroflaxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammat ries e.g. prednisolone, betamethasone, dexamethasone, carprofen,

ketoprofen; dietary supplements, .g. gamma-linoleic acid; and emollients. Ther fore, the invention further provides a product containing a compound of the invention and a compound from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of dis ases m diated *via* opiat rec ptors.

[0083] Th skilled person will also appr ciate that compounds of the invention may be tak n as a single dose on an "as required" basis (i.e. as needed or desired).

[0084] Thus, according to a further aspect f the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention in admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

[0085] Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

[0086] The biological activities of the compounds of the present invention were determined by the following test method.

Biological Test

[0087] Compounds of the present invention have been found to display activity in binding assays selective for the mu opioid receptor in dog brain. The assays were conducted by the following procedure.

[0088] Laboratory bred beagles were used as a source of dog brain tissue. Animals were euthanised, their brains removed and the cerebellum discarded. The remaining brain tissue was sectioned into small pieces approximately 3 g in weight and homogenised in 50 mM Tris pH 7.4 buffer at 4°C using a Kinematica Polytron™ tissue homogeniser. The resulting homogenate was centrifuged at 48,400 x g for 10 minutes and the supernatant discarded. The pellet was resuspended in Tris buffer and incubated at 37°C for 10 minutes. Centrifugation, resuspension and incubation steps were repeated twice more, and the final pellet was resuspended in Tris buffer and stored at -80°C. Membrane material prepared in this manner could be stored for up to four weeks prior to use.

[0089] For mu assays, increasing concentrations of experimental compound, (5×10^{-12} to 10^{-5} M), Tris buffer and ^3H ligand, ([D-Ala^2,N-Me-Phe^4,Gly-ol^5]-Enkephalin, DAMGO), were combined in polystyrene tubes. The reaction was initiated by the addition of tissue, and the mixture was incubated at room temperature for 90 minutes. The reaction was terminated by rapid filtration using a Brandel Cell Harvester™ through Betaplate™ GF/A glass fibre filters pre-soaked in 50 mM Tris pH 7.4, 0.1 % polyethylenimine buffer. The filters were then washed three times with 0.5 mL ice-cold Tris pH 7.4 buffer. Washed filters were placed in bags and Starscint™ scintillant added. Bags containing the filters and scintillant were heat sealed and counted by a Betaplate™ 1204 beta counter.

[0090] Duplicate samples were run for each experimental compound and the data generated was analysed using IC_{50} analysis software in Graphpad Prism. Ki values were calculated using Graphpad Prism according to the following formula:

$$Ki = IC_{50} / 1 + [^3H \text{ ligand}] / K_D$$

where IC_{50} is the concentration at which 50% of the ^3H ligand is displaced by the test compound and K_D is the dissociation constant for the ^3H ligand at the receptor site.

[0091] The invention is illustrated by the following Examples and Preparations in which the following abbreviations may be used:

APCI = atmospheric pressure chemical ionisation
br (in relation to NMR) = broad
CI = chemical ionisation
DMF = *N,N*-dimethylformamide
DMSO = dimethylsulfoxide
d (in relation to time) = day
d (in relation to NMR) = doublet
dd (in relation to NMR) = doublet of doublets
EtOAc = ethyl acetate
EtOH = ethanol
h = hour(s)
m (in relation to NMR) = multiplet
MeOH = methanol
min = minute

q (in relation to NMR) = quartet
q[i] (in r lation to NMR) = quint t
s (in relation to NMR) = singlet
t (in relation to NMR) = triplet
THF = tetrahydrofuran

[0092] For purifications by HPLC, combination and evaporation of appropriate fractions, determined by analytical HPLC, provided the desired compounds as acetate salts.

[0093] Analytical HPLC conditions used to highlight appropriate fractions were Phenomenex Magellan™ column, 4.6 x 150 mm, packed with 5μ C_{18} silica, eluting with a gradient of acetonitrile : 0.1 M aqueous heptanesulfonic acid (10:90 to 90:10 over 30 min, followed by a further 10 min at 90:10) at 1 mL per minute. Column oven temperature was 40°C, and ultraviolet detection of components was made at 220 nM.

[0094] When column chromatography is referred to this usually refers to a glass column packed with silica gel (40-63 μm). Pressure of ~165 kPa is generally applied and the ratio of crude product : silica gel required for purification is typically 50:1. Alternatively, an Isolute™ SPE (solid phase extraction) column or Waters Sep-Pak™ cartridge packed with silica gel may be used under atmospheric pressure. The ratio of crude product to silica gel required for purification is typically 100:1.

[0095] The hydrochloride salt may be made by methods commonly known to those skilled in the art of synthetic chemistry. Typically, to a solution of free base in dichloromethane (1 g : 100 mL) was added ethereal hydrochloric acid (1.0 M, 1.2 equivalent), the excess solvent was decanted off and the remaining precipitate was washed three times with ether and then dried *in vacuo*.

[0096] Nuclear magnetic resonance (NMR) spectral data were obtained using a Brucker AC3000, Brucker AM300, Varian Unity 300 or Varian Unity 400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. Mass spectral (MS) data were obtained on a Finnigan Masslab Navigator, a Fisons Instruments Trio 1000, a Fisons Instruments Trio 1000 APCI, or a Micromass Platform LC spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

<u>Examples</u>

Example 1: *Trans*-(±)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-1,2,3-benzotriazole

[0097] To a solution of *trans*-(±)-*N*-[2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenyl]acetamide (Preparation 3, 53 mg, 0.153 mmol) in ethanol (1 mL) was added concentrated hydrochloric acid (0.2 mL) and the mixture cooled in an ice bath. A solution of sodium nitrite (21 mg, 0.31 mmol) in water (0.1 mL) was added dropwise and stirring continued for 3 hours at this temperature. A further portion of hydrochloric acid (0.1 mL) was added and the reaction refluxed for 3 hours. The reaction mixture was cooled and diluted with ethyl acetate (100 mL) and water (50 mL), and then washed with saturated sodium bicarbonate solution (50 mL). The separated organic phase was washed with brine (25 mL) and both aqueous phases extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) then concentrated *in vacuo*. The residue was triturated with hexane twice then dried on a vacuum pump to give the benzotriazole (44 mg) as a pale yellow solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.70 (3H, d), 0.85 (3H, m), 1.40 (3H, s), 7.40 (1H, d), 7.70 (1H, s) and 7.85 (1H, d).
MS (Thermospray): M/Z (MH^+) 315.3; $C_{19}H_{30}N_4$ +H requires 315.5.

Example 2: *Trans*-(±)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0098] A solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 150 mg, 0.494 mmol) in 90% formic acid (1.0 mL) was heated to 100°C for 2 hours. The reaction was diluted with water (50 mL) and poured into ethyl acetate (50 mL) and 2 *N* sodium hydroxide (25 mL). The organic layer was washed with brine (25 mL) and both aqueous layers extracted with ethyl acetate (50 mL). The combined organics were dried ($MgSO_4$) and then concentrated *in vacuo* to give the benzimidazole (130 mg) as a light brown oil. This was dissolved in diethyl ether (1.0 mL) and treated with 1 *N* HCl in diethyl ether (0.46 mL, 0.46 mmol), which was added dropwise. The solvent was removed *in vacuo* to give the hydrochloride as a light brown solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (3H, d), 0.90 (3H, m), 1.35 (3H, s), 7.25 (1H, d), 7.50 (1H, s), 7.60 (1H, d) and 8.00 (1H, s).
MS (Thermospray): M/Z (MH^+) 313.8; $C_{20}H_{30}N_3$ +H requir s 313.5.

Example 3: *Trans*-(±)-2-methyl-5-(1-h xyl-3,4-dimethyl-4-pip ridinyl)-1*H*-benzimidazole

[0099] A solution of *trans*-(±)-*N*-[2-amino-5-(1-hexyl-3,4-dimethyl-4-pip ridinyl)-phenyl]acetamid (Preparation 3, 150 mg, 0.434 mmol) in acetic acid (2.0 mL) was heated to reflux for 2 hours. The r action was diluted with water (25 mL) and ethyl acetate (50 mL) then wash d with 2 *N* sodium hydroxide solution (50 mL). The separated organic phase was wash d with brine (50 mL). Both aqueous phases were xtracted with ethyl acetate (50 mL) and the combined organics dried ($MgSO_4$) then concentrated *in vacuo*. The crude residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (95:5) as the eluant to give the benzimidazole (71 mg) as a pale yellow oil. This was dissolved in diethyl ether (1 mL) and treated with 1 *N* HCl in diethyl ether (0.2 mL, 0.2 mmol). The solvent was removed *in vacuo* to give the hydrochloride as pale brown solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 0.85 (3H, m), 1.35 (3H, s), 2.60 (3H, s), 7.20 (1H, d) and 7.40-7.50 (2H, br s).
MS (Cl): M/Z (MH^+) 328.5; $C_{21}H_{33}N_3$ +H requires 328.5.

Example 4: *Trans*-(±)-2-(trifluoromethyl)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0100] A solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 25 mg, 82 µmol) in trifluoroacetic acid (1 mL) was refluxed for 2 hours. The cooled reaction was diluted with water (25 mL) and ethyl acetate (50 mL) then washed with 2 *N* sodium hydroxide solution (25 mL). The organic layer was washed with brine (25 mL) and both aqueous layers back-extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : methanol (90:10) as eluant to give the benzimidazole (29 mg) as a pale yellow oil. This was dissolved in diethyl ether (1 mL) and treated with 1 *N* HCl in diethyl ether (84 µL, 84 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a light brown solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 0.85 (3H, m), 1.40 (3H, s), 7.35 (1H, d), 7.55 (1H, s) and 7.65 (1H, d).
MS (Cl): M/Z (MH^+) 382.4; $C_{21}H_{30}F_3N_3$ +H requires 382.5.

Example 5: *Trans*-(±)-6-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-indole

[0101] To a solution of *trans*-(±)-2-[2-(trimethylsilyl)ethynyl]-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)aniline (Preparation 7, 211 mg, 0.55 mmol) in *N,N*-dimethylformamide (2 mL) under nitrogen was added copper(I) iodide (208 mg, 1.09 mmol) and the reaction mixture heated to 100°C for 1.5 hours. The cooled reaction was diluted with diethyl ether and filtered through Celite®. The filtrate was washed with brine and the separated aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel using a gradient of dichloromethane : ethanol : ammonium hydroxide (300:8:1 to 200:8:1) to give the indole (51 mg) as an oil. This was dissolved in dichloromethane and treated with 1 *N* HCl in diethyl ether (2 mL). The solvent was removed *in vacuo* to give the hydrochloride as a light yellow solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (3H, s), 0.90 (3H, m), 1.35 (3H, s), 6.50 (1H, s), 7.10 (1H, d), 7.15 (1H, m), 7.25 (1H, m), 7.60 (1H, d) and 8.05 (1H, br s).
MS (Cl): M/Z (MH^+) 313.4; $C_{21}H_{32}N_2$ +H requires 313.5.

Example 6: *Trans*-(±)-2-isopropyl-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0102] A solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 36 mg, 0.119 mmol) in isobutyric acid (1 mL) was refluxed for 4 hours. The cooled reaction was diluted with water (25 mL) and ethyl acetate (50 mL) then washed with 2 *N* sodium hydroxide solution (25 mL). The organic layer was washed with brine (25 mL) and both aqueous layers back-extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (97:3) as eluant to give the benzimidazole (3 mg) as a colourless oil. This was dissolved in diethyl ether (0.5 mL) and treated with 1 *N* HCl in diethyl ether (9 µL, 9 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a reddish solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (3H, d), 0.90 (3H, m), 1.30 (3H, s), 1.45 (6H, d) and 6.70-7.20 (3H, m).
MS (Thermospray): M/Z (MH^+) 356.2; $C_{23}H_{37}N_3$ +H requires 356.5.

Example 7: *Trans*-(±)-2-methoxy-5-(1-h xyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0103] A mixture containing *trans*-(±)-4-(1-h xyl-3,4-dimethyl-4-pip ridinyl)-1,2-benzenediamine (Preparation 5, 33 mg, 0.109 mmol), tetramethoxymethane (1 mL) and glacial acetic acid (7 mL) was stirred at room temp rature for 2 hours then refluxed for a further 2 hours. The r action mixture was concentrated *in vacuo,* dissolved in ethyl ac tate (50 mL) and then washed with saturated potassium carbonate solution (25 mL) and brine (25 mL). Each of the aqueous phases were extracted with ethyl acetate (25 mL) and the combined organics dried ($MgSO_4$) and then concentrated *in vacuo.* The residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (97:3) as eluant to give the benzimidazole (5 mg) as a colourless oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, d), 0.90 (3H, s), 1.35 (3H, s), 4.15 (3H, s) and 6.85-7.10 (3H, m).
MS (CI): M/Z (MH+) 344.4; $C_{21}H_{33}N_3O$ +H requires 344.5.

Example 8: *Trans*-(±)-2-cyclobutyl-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0104] A stirred solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 58 mg, 0.19 mmol) in cyclobutanecarboxylic acid (1 mL, 10 mmol) was heated at 145°C for 2 hours. The cooled reaction mixture was treated with 2 *N* sodium hydroxide solution (20 mL) and back-extracted with dichloromethane. The combined organics were dried ($MgSO_4$) and then concentrated *in vacuo* to give a black oil. The crude residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (99:1) as eluant to give the benzimidazole (47 mg) as a pale yellow oil. The oil was dissolved in dry diethyl ether (1 mL) and treated with a solution of 1 *N* HCl in diethyl ether (128 µL, 128 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a purple solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (d, 3H), 0.85 (m, 3H), 1.30 (s, 3H), 3.75 (q, 1H), 7.18 (m, 2H), 7.25 (s, 1H) and 7.50 (br s, 1H).
MS (Thermospray): M/Z (MH^+) 368.3; $C_{24}H_{37}N_3$ +H requires 368.3.

Example 9: *Trans*-(±)-2-benzyl-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0105] A stirred solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 48 mg, 0.16 mmol) in phenylacetic acid (1 mL, 8 mmol) was heated at 190°C for 2 hours. The cooled reaction mixture was treated with 2 *N* sodium hydroxide solution (20 mL) and back-extracted with dichloromethane. The combined organics were dried ($MgSO_4$) then concentrated *in vacuo* to give a black oil. The oil was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (99:1) as eluant to give the benzimidazole (31 mg) as a pale yellow oil. The oil was dissolved in dry diethyl ether (1 mL) and treated with a solution of 1 *N* HCl in diethyl ether (77 µL, 77 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a white solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (d, 3H), 0.90 (m, 3H), 1.30 (s, 3H), 4.25 (m, 2H), 7.10-7.40 (m, 8H) and 7.60 (br s, 1H).
MS (Thermospray): M/Z (MH^+) 404.2 ; $C_{27}H_{37}N_3$ +H requires 404.3.

Example 10: *Trans*-(±)-2-cyclopentyl-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0106] A stirred solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 49 mg, 0.161 mmol) in cyclopentanecarboxylic acid (1 mL) was heated at reflux for 2 hours. The cooled reaction was diluted with ethyl acetate (25 mL) and washed with 2 *N* sodium hydroxide solution (25 mL). The separated organic phase was washed with brine (25 mL) and each of the separated aqueous phases extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) and then concentrated *in vacuo.* The crude residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (99:1) as eluant to give the benzimidazole (19 mg) as a pale yellow oil. The oil was dissolved in diethyl ether (1 mL) and treated with a solution of 1 *N* HCl in diethyl ether (55 µL, 55 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a purple solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 0.85 (3H, m), 1.30 (3H, s), 3.30 (1H, q), 7.20 (1H, d) and 7.60 (2H, m).
MS (Thermospray): M/Z (MH^+) 382.3; $C_{25}H_{39}N_3$ +H requires 382.6.

Example 11: *Trans*-(±)-2-(difluoromethyl)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0107] A solution f *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-b nz nediamine (Pr paration 5, 55 mg, 0.181 mmol) in difluoroacetic acid (1 mL) was r fluxed for 4 hours. The cooled reaction was diluted with water (25 mL)

and thyl acetate (50 mL) then washed with 2 *N* sodium hydroxide solution (25 mL). The organic layer was washed with brine (25 mL) and both aqueous layers back-extracted with ethyl acetate (25 mL). The combin d organics wer dried ($MgSO_4$) then concentrated *in vacuo*. The r sidue was chromatographed on Merck 230-400 m sh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in m thanol (97:3) as luant to give the benzimidazol (47 mg) as a pal yellow oil. This was dissolved in diethyl ether (1 mL) and treated with 1 *N* HCl in diethyl ether (142 µL, 142 µmol). The solvent was remov d *in vacuo* to give the hydrochloride as a pale yellow solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (3H, d), 0.85 (3H, m), 1.40 (3H, s), 6.85 (1H, t), 7.30 (1H, d) and 7.60 (2H, m).
MS (Thermospray): M/Z (MH^+) 364.2; $C_{21}H_{31}F_2N_3$ +H requires 364.5.

Example 12: *Trans*-(±)-2-ethyl-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0108] A solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 55 mg, 0.181 mmol) in propionic acid (1 mL) was refluxed for 4 hours. The cooled reaction was diluted with water (25 mL) and ethyl acetate (50 mL) then washed with 2 *N* sodium hydroxide solution (25 mL). The organic layer was washed with brine (25 mL) and both aqueous layers back-extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (99:1) as eluant to give the benzimidazole (30 mg) as a pale yellow oil. This was dissolved in diethyl ether (1 mL) and treated with 1 *N* HCl in diethyl ether (100 µL, 100 µmol). The solvent was removed *in vacuo* to give the hydrochloride as a pale yellow solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 0.85 (3H, m), 1.35 (3H, s), 1.40 (3H, t), 2.90 (2H, q), 7.20 (1H, d) and 7.50 (2H, m).
MS (Thermospray): M/Z (MH^+) 342.1; $C_{22}H_{34}N_3$ +H requires 342.5.

Example 13: *Trans*-(±)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one

[0109] A mixture of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 195 mg, 0.643 mmol), urea (244 mg, 4.07 mmol) and *N,N*-dimethylformamide (2.1 mL) was heated to reflux for 5 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (25 mL) and water (25 mL). The organic phase was extracted with brine (25 mL) and each separated aqueous phase extracted with ethyl acetate (25 mL). The combined organics were dried ($MgSO_4$) then concentrated *in vacuo*. The crude product was chromatographed on Merck 230-400 mesh silica gel (10 g) using ethyl acetate : 2 *N* ammonia in methanol (97:3) as eluant to give the benzimidazolone (30 mg) as a pale brown solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 0.90 (3H, m), 3.30 (1H, br s) and 7.00 (3H, m).
MS (Thermospray): M/Z (MH^+) 330.1; $C_{20}H_{30}N_3O$ +H requires 330.5.

Example 14: *Trans*-(±)-*N*-[5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazol-2-yl]methanesulfonamide

[0110] To a solution of *trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 5, 1.05 g, 3.46 mmol) in toluene (30 mL) under an atmosphere of nitrogen was added a solution of *N*-methanesulfonylcarbonimidic acid dichloride ([Neidlein and Haussmann, *Tetrahedron Lett.*, **1965**, 1753] 0.61 g, 3.46 mmol) in toluene (5 mL). The reaction was heated at 85°C for 5 hours then cooled to room temperature and allowed to stand under an atmosphere of nitrogen overnight. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (50 mL) and saturated sodium bicarbonate solution (50 mL), which mixture was stirred for 1 hour. The organic layer was separated and the aqueous washings were extracted with dichloromethane (2 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a dark green-black solid. The residue was chromatographed on Merck 230-400 mesh silica gel (50 g) eluting hexane : ethyl acetate (40:60 to 20:80), basified with 3 drops of concentrated ammonium hydroxide, to give the sulfonamide (495 mg) as a yellow solid.
NMR δ_H(300 MHz, CD_3OD) (selected data from free base): 0.75 (3H, d), 0.90 (3H, t), 1.30-1.40 (9H, m), 1.45-1.6 (2H, m), 1.70 (1H, m), 2.10 (1H, m), 2.25-2.50 (4H, m), 2.55-2.70 (2H, m), 2.85 (1H, m), 3.00 (3H, s) and 7.15-7.25 (3H, m).
MS (Electrospray): M/Z (MH^+) 407.2; $C_{21}H_{34}N_4O_2S$ +H requires 407.3.

Example 15: *Trans*-(±)-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazol-2-ylamine

[0111] A solution of *trans*-(±)-*N*-[5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazol-2-yl]methanesulfonamide (Example 14, 150 mg, 3.22 mmol) in 48 % hydrobromic acid (5 mL) and glacial acetic acid (5 mL) was reflux d for 48 hours. The reaction mixture was cooled and basifi d to pH 10 with 2 *N* sodium hydroxide solution. The product was extracted with dichloromethane (3 x 25 mL) and the solv nt was dried (Na_2SO_4). The crud r sidue was chromato-

graph d on Merck 230-400 mesh silica gel (8 g) eluting with ethyl acetate-dichloromethane (20:80). The starting ma-t rial was collected from the column, before flushing with methan l : dichloromethane (40:60). Th residue was concentrated *in vacuo* then r dissolved in dichloromethane (30 mL). The solv nt was dri d (Na_2SO_4), filtered and concentrated *in vacuo* to give the benzimidazolamine (15 mg) as a light brown solid.
NMR δ_H(300 MHz, CD_3OD) (selected data from free base): 0.80 (3H, d), 0.90 (3H, t), 1.80 (1H, m), 2.20 (1H, m), 2.40 (1H, m), 2.90 (1H, m), 6.95 (1H, d) and 7.10-7.20 (2H, m).
MS (Electrospray): M/Z (MH^+) 329.2; $C_{20}H_{32}N_4$ +H requires 329.3.

Example 16: *Trans*-(±)-2-(trifluoromethyl)-5-[1-(3-phenylpropyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0112] A solution of *trans*-(±)-2-(trifluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 11, 100 mg, 0.34 mmol) in *N,N*-dimethylformamide (3 mL) was treated with sodium bicarbonate (45 mg, 0.54 mmol) and then 1-bromo-3-phenylpropane (82 µL, 108 mg, 0.54 mmol). The reaction was heated at 80°C for 6 hours and the solvent was removed by evaporation *in vacuo*. The residue was partitioned between dichloromethane and water. The organic solvent was dried (Na_2SO_4) and the solvent removed by evaporation *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (5 g) using a gradient of ethyl acetate : hexane : ammonium hydroxide (39: 60:1 to 49:50:1) to give the benzimidazole (28 mg) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (d, 3H), 1.40 (s, 3H) and 7.10-7.30 (m, 8H).
MS (Thermospray): M/Z (MH^+) 416.2; $C_{24}H_{28}F_3N_3$ +H requires 416.5.

Example 17: *Trans*-(±)-2-(trifluoromethyl)-5-[1-(2-phenoxyethyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0113] A solution of *trans*-(±)-2-(trifluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 11, 50 mg, 0.17 mmol) in *N,N*-dimethylformamide (2 mL) was treated with sodium bicarbonate (23 mg, 0.27 mmol) and then β-bromophenetole (38 mg, 0.19 mmol). The reaction was heated at 60°C for 6 hours then stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and water. The organic solvent was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (5 g) using a gradient of ethyl acetate : hexane : ammonium hydroxide (0:99:1 to 49:50:1) to give the benzimidazole (20 mg) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (d, 3H), 1.30 (s, 3H), 3.50 (m, 1H), 4.10 (m, 2H), 4.20 (m, 1H), 6.60 (m, 2H), 6.90 (m, 4H) and 7.30 (m, 2H).
MS (Thermospray): M/Z (MH^+) 418.4; $C_{23}H_{26}F_3N_3O$ +H requires 418.5.

Example 18: *Trans*-(±)-2-(trifluoromethyl)-5-[1-(3-methylphenethyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0114] A solution of *trans*-(±)-2-(trifluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 11, 51 mg, 0.17 mmol) in *N,N*-dimethylformamide (2 mL) was treated with sodium bicarbonate (28 mg, 0.33 mmol) and then 1-(2-bromoethyl)-3-methylbenzene (37 mg, 0.19 mmol). The reaction was heated to 60°C for 24 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent evaporated *in vacuo*. The residue was chromatographed n Merck 230-400 mesh silica gel (5 g) using a gradient of ethyl acetate : hexane : ammonium hydroxide (10:89:1 to 50:49:1) to give the benzimidazole (5 mg) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (m, 3H), 1.30 (s, 3H), 2.30 (s, 3H), 3.40 (t, 1H), 6.60 (m, 2H), 7.00 (m, 3H) and 7.10-7.20 (m, 2H).
MS (Thermospray): M/Z (MH^+) 416.4; $C_{24}H_{28}F_3N_3$ +H requires 416.5.

Example 19: *Trans*-(±)-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0115] A solution of *trans*-(±)-*N*-[2-amino-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]formamide (Preparation 14, 98 mg, 0.29 mmol) in formic acid (11 mL) was refluxed for 6 hours and made basic by addition of 2 *N* sodium hydroxide solution. The aqueous layer was washed ethyl acetate (30 mL) and the organic layer dried (Na_2SO_4) then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (10 g), using methanol : dichloromethane : ammonium hydroxide (10:89:1) as eluant to give the benzimidazole (72 mg) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (s lected data from free base): 0.70 (d, 3H), 1.40 (s, 3H), 2.40 (d, 2H), 2.50 (s, 2H), 2.90 (m, 1H), 3.50 (d, 1H), 3.60 (d, 1H), 7.20-7.40 (m, 7H) and 7.50-7.60 (m, 2H).
MS (Thermospray): M/Z (MH^+) 320.8; $C_{21}H_{25}N_3$ +H requir s 320.5.

Example 20: *Trans*-(±)-5-[1-(2-propoxyethyl)-3,4-dim thyl-4-piperidinyl]-1*H*-b nzimidazol

[0116] A solution of *trans*-(±)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 15, 30 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) was treated with 2-chloroethylpropyl ether (17 mg, 0.14 mmol) and then sodium bicarbonate (25 mg, 0.3 mmol) and a catalytic amount of sodium iodide. The mixture was heat d at 60°C for 6 hours. The reaction mixture was partiti ned between sodium bicarbonate solution (10 mL) and diethyl ther (10 mL). The separated organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The title compound was purified by preparative HPLC on a Phenomenex Magellen™ column, 150 mm x 21 mm; Flow 20 mL min^{-1}; employing UV detection at 220 nm; eluant acetonitrile : 0.1 M aqueous ammonium acetate (30:70 to 95:5 over 10 minutes).
MS (Thermospray): M/Z (MH+) 316.3; $C_{19}H_{29}N_3O$ +H requires 316.5.

Example 21: *Trans*-(±)-5-[1-(5-methylhexyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0117] A solution of *trans*-(±)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 15, 30 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) was treated with 1-bromo-5-methylhexane (25 mg, 0.14 mmol), followed by sodium bicarbonate (25 mg, 0.3 mmol). The reaction was heated to 60°C for 6 hours. The reaction was partitioned between saturated sodium bicarbonate solution (10 mL) and diethyl ether (10 mL). The separated organic phase was dried (Na_2SO_4) and the solvent was removed by evaporation *in vacuo*. The title compound was purified by preparative HPLC on a Phenomenex Magellen™ column, 150 mm x 21 mm; Flow 20 mL min^{-1}; employing UV detection at 220 nm; eluant acetonitrile : 0.1 M aqueous ammonium acetate (30:70 to 95:5 over 10 minutes).
MS (Thermospray): M/Z (MH+) 328.3; $C_{21}H_{33}N_3$ +H requires 328.5.

Example 22: *Trans*-(±)-2-(difluoromethyl)-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0118] A solution of *trans*-(±)-4-(1-benzyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine (Preparation 16, 2.00 g, 6.46 mmol) in difluoroacetic acid was refluxed for 4 hours. The reaction mixture was cooled and diluted with water (50 mL) and ethyl acetate (50 mL). The mixture was treated with 2 *N* sodium hydroxide solution and shaken until the aqueous layer was basic. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 75 mL). The combined organics were washed once with saturated brine (100 mL) and dried (Na_2SO_4). The solvent was concentrated *in vacuo* to give a brown gum (2.8 g). The residue was chromatographed on Merck 230-400 mesh silica gel (75 g) eluting with ethyl acetate : hexane (50:50). The product was collected as a yellow syrup which solidified under vacuum (2.3 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 1.35 (3H, s), 3.45 (1H, d), 3.65 (1H, d), 6.85 (1H, t), 7.20-7.40 (7H, m), 7.75 (1H, m) and 9.85-10.05 (1H, br s).
MS (Electrospray): M/Z (MH+) 370.0; $C_{22}H_{25}F_2N_3$ +H requires 370.2.

Example 23: *Trans*-(±)-2-(difluoromethyl)-5-(1-pentyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0119] A solution of *trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 17, 50 mg, 0.18 mmol) in methanol (4 mL) was cooled to 0°C and treated with valeraldehyde (16 mg, 20 µL, 0.18 mmol) and sodium triacetoxyborohydride (53 mg, 0.25 mmol). The solution was left to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (75 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried (Na_2SO_4) and then concentrated *in vacuo* to give a clear gum. The residue was purified on a silica (5 g) Sep-Pak™ eluting with ethyl acetate : hexane (20:80) to give the title compound as a clear glass (29 mg).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (3H, d), 0.90 (3H, t), 1.35 (3H, s), 2.55-2.70 (2H, m), 2.95 (1H, m), 6.85 (1H, t), 7.35 (1H, d) and 7.45-7.65 (2H, m).
MS (Electrospray): M/Z (MH+) 350.1; $C_{20}H_{29}F_2N_3$ +H requires 350.2.

Example 24: *Trans*-(±)-2-(difluoromethyl)-5-[1-(2-benzyloxyethyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0120] A solution of *trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 17, 50 mg, 0.18 mmol) in methanol (4 mL) was cooled to 0°C and treated with benzyloxyacetaldehyde (27 mg, 0.18 mmol) and sodium triacetoxyborohydride (53 mg, 0.25 mmol). The solution was left to warm to room temp rature and stirr d for 16 hours. The reaction mixture was c ncentrated *in vacuo* and th residue was partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (75 mL). Th organic layer was s parat d and the aqueous layer

was xtracted with thyl acetate (3 x 50 mL). The combined organics wer dried (Na_2SO_4) and then concentrated *in vacuo* to giv a clear gum. The residue was purifi d on a silica (5 g) Sep-Pak™ eluting with ethyl ac tate : hexane (20:80) to give an off-white solid (32 mg).

NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (3H, d), 1.35 (3H, s), 3.65 (2H, t), 4.55 (2H, s), 6.90 (1H, t), 7.20-7.35 (5H, m) and 7.40-7.75 (3H, m).

MS (Electrospray): M/Z (MH+) 414.1; $C_{24}H_{29}F_2N_3O$ +H requires 414.2.

Example 25: *Trans*-(±)-2-(difluoromethyl)-5-[1-(2-phenoxyethyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0121] A solution of *trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 17, 50 mg, 0.18 mmol) in methanol (4 mL) was cooled to 0°C and treated with 2-phenoxyacetaldehyde (25 mg, 0.18 mmol) and sodium triacetoxyborohydride (53 mg, 0.25 mmol). The solution was left to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (75 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried (Na_2SO_4) and then concentrated *in vacuo* to give a clear gum. The residue was purified on a silica (5 g) Sep-Pak™ eluting with ethyl acetate : hexane (20:80) to yield the title compound as a white solid (19 mg).

NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d) 1.35 (3H, s), 4.10 (2H, t), 6.85 (1H, t), 6.80-6.95 (2H, m), 7.25-7.55 (5H, m) and 7.75 (1H, m).

MS (Thermospray): M/Z (MH+) 400.1; $C_{23}H_{27}F_2N_3O$ +H requires 400.2.

Example 26: *Trans*-(±)-2-(difluoromethyl)-5-[1-(3-phenoxypropyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0122] A solution of *trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 17, 50 mg, 0.18 mmol) in methanol (4 mL) was cooled to 0°C and treated with 3-phenoxypropanal (27 mg, 0.18 mmol) and sodium triacetoxyborohydride (53 mg, 0.25 mmol). The solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (75 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried (Na_2SO_4) and then concentrated *in vacuo* to give a clear gum. The residue was purified on a silica (5 g) Sep-Pak™ eluting with ethyl acetate : hexane (20:80) to yield the title compound as an off-white gum (20 mg).

NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 1.35 (3H, s), 4.05 (2H, t), 6.90 (1H, t), 6.85-6.95 (3H, m) and 7.20-7.40 (4H, m).

MS (Electrospray): M/Z (MH+) 414.1; $C_{24}H_{29}F_2N_3O$ +H requires 414.2.

Example 27: *Trans*-(±)-2-(difluoromethyl)-5-[1-(4-methylphenethyl)-3,4-dimethyl-4-piperidinyl]-1*H*-benzimidazole

[0123] A solution of *trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Preparation 17, 50 mg, 0.18 mmol) in methanol (4 mL) was cooled to 0°C and treated with 2-(4-methylphenyl)-acetaldehyde (24 mg, 0.18 mmol) and sodium triacetoxyborohydride (53 mg, 0.25 mmol). The solution was left to warm to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (75 mL) and saturated sodium bicarbonate solution (75 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried (Na_2SO_4) and then concentrated *in vacuo* to give a clear gum. The residue was purified on a silica (5 g) Sep-Pak™ eluting with ethyl acetate : hexane (20:80) to give the title compound as a light brown gum (16 mg).

NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (3H, d), 1.35 (3H, s), 2.35 (3H, s), 2.95 (1H, m), 6.90 (1H, t), 6.95-7.05 (3H, m), 7.35 (1H, m) and 7.75 (1H, m).

MS (Electrospray): M/Z (MH+) 398.1; $C_{24}H_{29}F_2N_3$ +H requires 398.2.

Example 28: *Trans*-(±)-2-methyl-6-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,3-benzoxazole

[0124] To a stirred solution of *trans*-(±)-2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 19, 194 mg, 0.637 mm l), triethylamine (98 µL, 0.701 mmol) and acetyl chloride (50 µL, 0.701 mmol) in xylenes (10 mL) was added pyridinium *p*-toluenesulfonat (80 mg, 0.319 mmol) and the r action mixture was h ated to reflux overnight. Upon cooling, the reaction mixtur was diluted with water (100 mL) and xtracted with ethyl acetate (3 x 100 mL). The combined extracts were dried (Na_2SO_4) filter d and concentrated *in vacuo* to give th crude product which was purified

via silica gel chromatography eluting with a gradient of ethyl acetate: dichloromethane : ammonium hydroxide (150: 349:1 to 200:299:1) to give the title compound (117 mg) as a pale yellow oil.

NMR δ_H(400 MHz, C_6D_6) (selected data from fr e base): 0.86 (m, 6H), 1.19 (s, 3H), 1.21-1.34 (m, 7H), 1.43 (m, 2H), 1.78 (m, 1H), 2.08 (s, 3H), 2.09-2.35 (m, 4H), 2.45 (m, 2H), 2.68 (m, 1H), 7.06 (dd, 1H), 7.28 (d, 1H) and 7.61 (d, 1H).

MS (APCI+) : M/Z (MH+) 329.3; $C_{21}H_{32}N_2O$ +H requires 329.3.

Example 29: *Trans*-(±)-6-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,3-benzoxazole

[0125] To a stirred solution of *trans*-(±)-2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 19, 109 mg, 0.358 mmol), triethylamine (55 µL, 0.394 mmol) and triethyl orthoformate (66 µL, 0.394 mmol) in xylenes (10 mL) was added pyridinium *p*-toluenesulfonate (5 mg, 2 µmol) and the reaction mixture was heated to reflux overnight. Upon cooling, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product which was purified via silica gel chromatography eluting with ammonium hydroxide : methanol : dichloromethane (1:10:489) to give the title compound (76 mg) as a pale yellow oil.

NMR δ_H(400 MHz, C_6D_6) (selected data from free base): 0.79 (d, 3H), 0.86 (t, 3H), 1.15 (s, 3H), 1.23-1.33 (m, 7H), 1.46 (m, 2H), 1.75 (m, 1H), 2.06-2.31 (m, 4H), 2.39 (m, 2H), 2.66 (m, 1H), 7.02 (dd, 1H), 7.29 (m, 2H) and 7.66 (d, 1H).

MS (APCI+): M/Z (MH+) 315.3; $C_{20}H_{30}N_2O$ +H requires 315.2.

Example 30: *Trans*-(±)-2-ethyl-6-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,3-benzoxazole

[0126] To a stirred solution of *trans*-(±)-2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 19, 145 mg, 0.476 mmol), triethylamine (73 µL, 0.524 mmol) and propionyl chloride (46 µL, 0.524 mmol) in xylenes (10 mL) was added pyridinium *p*-toluenesulfonate (4 mg, 2 µmol) and the reaction mixture was heated to reflux for 120 h. Upon cooling, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product which was purified via silica gel chromatography eluting with ammonium hydroxide : methanol : dichloromethane (1:10:489) to give the title compound (89 mg) as a pale yellow oil.

NMR δ_H(400 MHz, C_6D_6) (selected data from free base): 0.85 (m, 6H), 1.12 (t, 3H), 1.20 (s, 3H), 1.22-1.36 (m, 7H), 1.44 (m, 2H), 1.79 (m, 1H), 2.09-2.36 (m, 4H), 2.45 (m, 2H), 2.52 (q, 2H), 2.69 (m, 1H), 7.04 (dd, 1H), 7.30 (d, 1H) and 7.64 (d, 1H).

MS (APCI+): M/Z (MH4) 343.3; $C_{21}H_{34}N_2O$ +H requires 343.3

Example 31: *Trans*-(±)-6-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,3-henzoxazol-2(3*H*)-one

[0127] To a stirred solution of *trans*-(±)-2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 19, 183 mg, 0.601 mmol) in *N,N*-dimethylformamide (3 mL) was added 1,1'-carbonyldiimidazole (107 mg, 0.661 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and then concentrated *in vacuo* to give the crude product which was purified via silica gel chromatography eluting with a gradient of methanol : dichloromethane : ammonium hydroxide (10:489:1 to 15:484:1) to give the title compound (82 mg) as a pale yellow oil.

NMR δ_H(400 MHz, C_6D_6) (selected data from free base): 0.81 (d, 3H), 0.85 (t, 3H), 1.10 (s, 3H), 1.23-1.30 (m, 7H), 1.44 (m, 2H), 1.67 (m, 1H), 2.07-2.45 (m, 6H), 2.72 (m, 1H), 6.62 (d, 1H), 6.76 (dd, 1H), 6.90 (d, 1H) and 8.15 (br s, 1H).

MS (APCI+): M/Z (MH+) 331.3; $C_{21}H_{30}N_2O$ +H requires 331.2.

Preparation of Starting Materials

Preparation 1: *Trans*-(±)-*N*-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenyl]acetamide

[0128] To a stirred solution of *trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)aniline (Preparation 23, 2.0 g, 6.93 mmol) in dichloromethane (56 mL) and triethylamine (14 mL) was added acetyl chloride (0.988 mL, 1.09 g, 13.9 mmol) dropwise. The turbid orange mixture was stirred for 60 hours at room temperature and the reaction partitioned between saturated sodium bicarbonate solution (50 mL) and dichloromethane (100 mL). The organic phase was washed with brine (50 mL) and both aqueous phases extracted with dichloromethane. The combined organics were dried ($MgSO_4$) then concentrated *in vacuo*. The crud r sidue was chromatographed on Merck 230-400 mesh silica gel (25 g) using ethyl acetate : 0.5 *N* ammonia in dioxan (98:2) as the eluant to give the amide (2.30 g) as an range oil.

NMR δ_H(300 MHz, $CDCl_3$) (sel cted data): 0.80 (3H, d), 0.90 (3H, t), 2.15 (3H, s) and 7.0-7.4 (4H, m).

MS (Thermospray): M/Z (MH^+) 331.6; $C_{21}H_{34}N_2O$ +H requir s 331.3.

Pr paration 2: *Trans*-(±)-*N*-[2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl) phenyl] a etamid

[0129] To a solution of *trans*-(±)-*N*-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenyl]acetamide (Preparation 1, 2.29 g, 6.93 mmol) in dry acetonitrile (45 mL), cooled in an ice bath, was added nitronium tetrafluoroborate (1.1 g, 7.62 mmol) portionwise. The reaction was stirred for 45 minutes and TLC (silica plate eluted with ethyl acetate) showed starting material remaining. A further portion of nitronium tetrafluoroborate (0.55 g, 3.81 mmol) was added and the reaction stirred for another 30 minutes, this process was repeated once more (two equivalents in total). The mixture was then poured into a saturated sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (50 mL). The organic phase was washed with brine (50 mL) and both separated aqueous phases extracted with ethyl acetate (50 mL). The combined organics were dried ($MgSO_4$) then concentrated *in vacuo*. The crude residue was chromatographed on Merck 230-400 mesh silica gel (25 g) using ethyl acetate as the eluant to give the nitrophenylacetamide (1.43 g) as an orange semi-solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, d), 0.90 (3H, t), 1.30 (3H, s), 2.30 (3H, s), 7.1 (1H, d), 8.15 (1H, d), 8.80 (1H, s) and 10.4 (1H, br s).
MS (Thermospray): M/Z (MH^+) 376.9; $C_{21}H_{33}N_3O_3$ +H requires 376.6.

Preparation 3: *Trans*-(±)-*N*-[2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenyl]acetamide

[0130] A solution of *trans*-(±)-*N*-[2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenyl]acetamide (Preparation 2, 1.43 g, 3.81 mmol) and 10% palladium on carbon (175 mg) in methanol (34 mL) was subjected to hydrogenation in a bomb at 415 kPa and room temperature for 48 hours. The mixture was filtered and the filtrate concentrated *in vacuo* to give the crude acetamide (1.4 g) as a yellow semi-solid.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, s), 0.90 (3H, t), 2.20 (3H, s), and 6.75-7.20 (4H, m).
MS (Thermospray): M/Z (MH^+) 345.3; $C_{21}H_{34}N_3O$ +H requires 346.5.

Preparation 4: *Trans*-(±)-2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)aniline

[0131] A solution of *trans*-(±)-*N*-[2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenyl]acetamide (Preparation 2, 1.81 g, 4.82 mmol) in Claisens alkali (5 mL) (17.6 g of KOH in 12.6 mL of water made up to 50 mL with methanol) was warmed to 100°C for 15 minutes. Hot water (5 mL) was added and the mixture heated for a further 15 minutes. The reaction was cooled and the methanol removed *in vacuo*. The reaction was partitioned between ethyl acetate (50 mL) and water (50 mL) and the separated aqueous layer extracted with ethyl acetate (50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) then concentrated in vacuo to give the crude nitroaniline (1.23 g) as an orange oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, s), 0.90 (3H, m), 6.10 (2H, br s), 6.60 (1H, s), 6.65 (1H, d) and 8.05 (1H, d).
MS (Thermospray): M/Z (MH^+) 334.3; $C_{19}H_{30}N_3O_2$ +H requires 334.5.

Preparation 5: *Trans*-(±)-4-(1-hexyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine

[0132] A mixture of *trans*-(±)-2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-aniline (Preparation 4, 1.23 g, 3.69 mmol) and 10% palladium on charcoal (151 mg) in ethanol (20 mL) was subjected to hydrogenation in a bomb at 415 kPa and room temperature for 48 hours. The mixture was filtered through Celite®, washing with methanol and the filtrate concentrated *in vacuo* to give the diamine as a dark brown oil. This compound was very sensitive to air oxidation and was stored cold under an inert atmosphere.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, d), 0.90 (3H, m) and 6.65 (3H, br s).
MS (Thermospray): M/Z (MH^+) 304.6; $C_{19}H_{33}N_3$ +H requires 304.5.

Preparation 6: *Trans*-(±)-2-iodo-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-aniline

[0133] To a solution of *trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)aniline (Preparation 23, 272 mg, 0.94 mmol) in glacial acetic acid (5 mL) was added iodine (478 mg, 1.89 mmol) and the reaction stirred overnight. Saturated sodium bicarbonate solution was added until effervescenc ceas d and the mixture diluted with dichlorom thane : methanol (100 mL, 10:1). The separated organic layer was washed with saturated sodium thiosulfate solution and then brine. The organic layer was dried ($MgSO_4$) then conc ntrat d *in vacuo*. The residue was chromat graphed on Merck 230-400 mesh silica g l using dichloromethan : ethanol : ammonium hydroxide (200:8:1) as th eluant to give the iodoaniline

(88 mg) as a yellow oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (3H, s), 0.90 (3H, m), 4.00 (2H, br s), 6.45 (1H, d), 6.70 (1H, s) and 7.50 (1H, d).
MS (Thermospray): M/Z (MH^+) 415.4; $C_{19}H_{31}IN_2$ +H requires 415.4.

Pr paration 7: *Trans*-(±)-2-[2-(trimethylsilyl)ethynyl]-5-(1-h xyl-3,4-dim thyl-4-pip ridinyl) anilin

[0134] To a solution of *trans*-(±)-2-iodo-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-aniline (Preparation 6, 271 mg, 0.656 mmol) in triethylamine (10 mL) under nitrogen at room temperature was added bis(triphenylphosphine)-palladium(II) chloride (23 mg, 33 μmol) and copper(I) iodide (6.2 mg, 33 μmol). Trimethylsilylacetylene (120 μL, 84 mg, 0.84 mmol) was added and the mixture heated to 60°C overnight. The cooled reaction was diluted with ethyl acetate (50 mL), filtered through a bed of Celite®, and the filtrate washed with brine. The organic layer was dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel using dichloromethane : ethanol : ammonium hydroxide (300:8:1) as eluant to give the trimethylsilylaniline (211 mg) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.10 (9H, s), 0.80 (3H, s), 0.90 (3H, m), 4.20 (2H, br s), 6.60 (2H, m) and 7.20 (1H, d).
MS (CI): M/Z (MH^+) 385.2; $C_{24}H_{40}N_2Si$ +H requires 385.7.

Preparation 8: *Trans*-(±)-*N*-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)-phenyl]acetamide

[0135] To a stirred solution of *trans*-(±)-3-(1-benzyl-3,4-dimethyl-4-piperidinyl)aniline (Preparation 27, 37.4 g, 0.15 mol) and triethylamine (70 mL, 0.50 mol) under nitrogen, was added dropwise acetyl chloride (17.4 mL, 0.244 mol). The reaction mixture was stirred for 12 hours at room temperature and then washed with a saturated solution of sodium bicarbonate (200 mL), which was then back-extracted with dichloromethane. The combined organics were dried ($MgSO_4$) then concentrated *in vacuo* to give a black oil (43 g). The crude oil was chromatographed on Merck 230-400 mesh silica gel (1 kg) using a gradient of CH_2Cl_2 : ethyl acetate : ammonium hydroxide (60:38:2 to 0:98:2) to give the acetamide (22 g) as a brown foam.
NMR δ_H(300 MHz, $CDCl_3$) (selected data): 0.80 (d, 3H), 1.30 (s, 3H), 2.15 (s, 3H), 3.50 (m, 2H) and 7.00-7.40 (m, 9H).
MS (Thermospray): M/Z (MH^+) 337.1; $C_{22}H_{28}N_2O$ +H requires 337.2.

Preparation 9: *Trans*-(±)-*N*-[2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]acetamide

[0136] A cooled (0°C) solution of *trans*-(±)-*N*-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]acetamide (Preparation 8, 3.7 g, 11 mmol) in acetonitrile (100 mL) was degassed five times by evacuation and then stirred under an atmosphere of nitrogen. Nitronium tetrafluoroborate (95%, 2.4 g, 16.6 mmol) was added portionwise and the reaction was stirred under nitrogen for 2 hours. The reaction was poured into saturated sodium bicarbonate solution (100 mL) and extracted into ethyl acetate (150 mL). The separated organic phase was dried ($MgSO_4$) then concentrated *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (150 g) using a gradient of hexane: ethyl acetate : ammonium hydroxide (50:49:1 to 0:99:1) to give the product (2.2 g) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (d, 3H), 1.30 (s, 3H), 2.30 (s, 3H), 3.40 (d, 1H), 3.60 (d, 1H), 7.10 (d, 1H), 7.20-7.40 (m, 5H), 8.10 (m, 1H) and 8.80 (m, 1H).
MS (Thermospray): M/Z (MH^+) 384.5; $C_{22}H_{27}N_3O_3$ +H requires 382.5

Preparation 10: *Trans*-(±)-2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl) aniline

[0137] A mixture of Claisens alkali (5 mL) (prepared from KOH (17.6 g) dissolved in water (12.6 mL) and diluted to 50 mL with methanol) and *trans*-(±)-*N*-[2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]-acetamide (Preparation 9, 2.20 g, 5.77 mmol) was heated on a steam bath for 30 minutes. Water (5 mL) was added and the reaction mixture was heated for a further 15 minutes. The reaction was cooled to room temperature and the methanol was removed by evaporation *in vacuo*. The residue was partitioned between water (15 mL) and dichloromethane (15 mL). The organic phase was then separated, dried (Na_2SO_4) and solvent removed by evaporation *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (75 g), eluting with a gradient of hexane: ethyl acetate : ammonium hydroxide (49:50:1 to 0:99:1), followed by ethyl acetate : ethanol : ammonium hydroxide (89:10:1), to give the product (1.2 g) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.80 (d, 3H), 1.30 (s, 3H), 3.40 (d, 1H), 3.60 (d, 1H), 6.00 (br s, 2H), 6.60 (m, 2H), 7.20-7.40 (m, 5H) and 8.00 (d, 1H).
MS (Thermospray): M/Z (MH^+) 340.3; $C_{20}H_{25}N_3O_2$ +H requires 340.4.

Preparation 11: *Trans*-(±)-2-(trifluor methyl)-5-(3,4-dim thyl-4-piperidinyl)-1*H*-b nzimidazole

[0138] A solution of *trans*-(±)-2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)-aniline (Pr paration 10, 1.1 g, 2.24 mmol) in di thyl eth r (3 mL) was treated with pyridine (0.18 mL, 2.24 mmol). The reaction was then cooled to 0°C, and trifluoroacetic acid (0.3 mL, 3.24 mmol) was added. Stirring under nitrogen was continued for 18 hours (during which time the reaction had warmed to room temperature), and the solvent then evaporated *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with water (3 x 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to give the crude product (1.3 g) as an orange oil (MS (Thermospray): M/Z (MH^+) 436.7; $C_{22}H_{24}N_3F_3O_3$ +H requires 435.5). This was dissolved in methanol (14 mL) and 10% palladium on carbon (Degussa E101, 168 mg) added. The reaction mixture was hydrogenated at 60°C, 415 kPa for 18 hours, after which it was filtered through a filter agent to remove the catalyst and the solvent was removed by evaporation *in vacuo* to give the crude product as a red-brown, glassy solid. This was used directly in the next step without further purification.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.90 (d, 3H), 1.40 (s, 3H), 1.80-2.40 (m, 5H), 3.10 (m, 2H) and 6.50-6.70 (m, 3H).
MS (Thermospray):M/Z (MH^+) 298.3; $C_{15}H_{18}F_3N_3$ +H requires 298.3.

Preparation 12: *Trans*-(±)-N-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)-phenyl]formamide

[0139] Oxalyl chloride (1.48 mL, 2.16 g, 17 mmol) in dichloromethane (9 mL) was added dropwise to an ice cold solution of imidazole (1.16 g, 17 mmol), triethylamine (4.71 mL, 3.43 g, 34 mmol) and formic acid (0.65 mL, 0.78 g, 17 mmol) in dichloromethane (27 mL). The reaction was stirred at room temperature for 15 minutes, at which time a white precipitate was observed, and a solution of *trans*-(±)-3-(1-benzyl-3,4-dimethyl-4-piperidinyl)aniline (5.0 g, 17.0 mmol) in dichloromethane (10 mL) was added dropwise. The reaction was then stirred at room temperature overnight, filtered to remove triethylamine hydrochloride and the filtrate washed with saturated sodium bicarbonate solution (30 mL), water (20 mL) and brine (10 mL). The solvent was removed *in vacuo* and the crude residue (5 g) chromatographed on Merck 230-400 mesh silica gel (150 g) using a gradient of hexane : ethyl acetate : ammonium hydroxide (50:49:1 to 25:74:1) to give the formamide (2.4 g) as an oil.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from a mixture of rotamers): 0.79 (3H, d), 1.33 (3H, s), 3.45 (1H, d), 3.60 (1H, d), 6.90-7.50 (9H, m), 8.40 (0.5H, s) and 8.64 (0.5H, d).
MS (CI): M/Z (MH^+) 323.2; $C_{21}H_{26}N_2O$ +H requires 323.4.

Preparation 13: *Trans*-(±)-*N*-[2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]formamide

[0140] To a stirred solution of *trans*-(±)-*N*-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]formamide (Preparation 12, 2.35 g, 7.3 mmol) in dry acetonitrile (45 mL) at 0°C was added nitronium tetrafluoroborate (1.07 g, 8.03 mmol) portion-wise over 5 minutes under nitrogen. After 1 hour, TLC (silica plate eluted with hexane : ethyl acetate : ammonium hydroxide, 50:49:1) showed incomplete reaction, and so a further portion of nitronium tetrafluoroborate (503 mg, 4.01 mmol) was added. After another 1 hour the reaction was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with saturated brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (3 g) was chromatographed on Merck 230-400 mesh silica gel (90 g) using a gradient of hexane : ethyl acetate : ammonium hydroxide (50:49:1 to 0:99:1) to give the nitrophenylformamide (1.1 g) as a brown gum.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from a mixture of rotamers): 0.80 (3H, d), 1.35 (3H, s), 3.45 (1H, d), 3.59 (1H, d), 7.10-7.40 (7H, m), 8.20 (1H, d), 8.60 (0.5, br s) and 8.80 (0.5H, br s).
MS (CI): M/Z (MH^+) 368.0; $C_{21}H_{25}N_3O_3$ +H requires 367.5.

Preparation 14: *Trans*-(±)-*N*-[2-amino-5-(1-benzyl-3,4-dimethyl-4-piperidinyl) phenyl] formamide

[0141] To a solution of *trans*-(±)-*N*-[2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenyl]formamide (Preparation 13, 164 mg, 0.42 mmol) in water : ethanol (15:85, 25 mL) was added iron powder (213 mg, 3.8 mmol) together with calcium chloride (24 mg, 0.21 mmol). The reaction was refluxed for two hours and the solvent was removed by evaporation *in vacuo*. The residue was partitioned between dichloromethane (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried (Na_2SO_4) and the solvent removed by vaporation *in vacuo*. The residue was chromatographed on Merck 230-400 mesh silica gel (10 g), using methanol : dichloromethane : ammonium hydroxide (10:89:1) as th eluant to give the amin phenylformamide (98 mg) as a pale yellow foam.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from fr base): 0.80 (d, 3H), 1.30 (s, 3H), 3.40 (d, 1H), 3.60 (d, 1H), 6.70 (t, 1H), 6.90-7.0 (m, 2H), 7.10-7.30 (m, 3H) and 8.40 (m, 1H).

MS (Thermospray): M/Z (MH^+) 338.6; $C_{21}H_{27}N_3O$ +H requires 338.5.

Pr paration 15: *Trans*-(±)-5-(3,4-dim thyl-4-piperidinyl)-1*H*-b nzimidazol

[0142] To a solution of *trans*-(±)-5-(1-benzyl-3,4-dim thyl-4-piperidinyl)-1*H*-benzimidazole (Example 19, 644 mg, 2.02 mmol) in methanol (10 mL) was added 10% palladium on carbon (Degussa E101, 113 mg) and th reaction was hydrogenated at 60°C and 415 kPa for 40 hours. The reaction mixture was filtered through a filter agent to remove the catalyst. The solvent was removed by evaporation *in vacuo* and the crude product (240 mg) was used directly in the next step without further purification.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.70 (d, 3H), 1.40 (s, 3H), 7.0-7.40 (m, 3H) and 8.00 (d, 1H).
MS (Thermospray): M/Z (MH^+) 230.1; $C_{14}H_{19}N_3$ +H requires 230.3.

Preparation 16: *Trans*-(±)-4-(1-benzyl-3,4-dimethyl-4-piperidinyl)-1,2-benzenediamine

[0143] A solution of *trans*-(±)-2-nitro-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)-aniline (Preparation 10, 5.8 g, 17.1 mmol) in ethanol (300 mL) was treated with iron powder (8.6 g, 153.9 mmol), calcium chloride (950 mg, 8.55 mmol) and water (88 mL). The reaction was then refluxed for 5 hours. A further portion of iron (4.3 g) and calcium chloride (475 mg) was added, and the reaction was refluxed for a further 3 hours. The reaction was cooled and filtered through a bed of Celite®. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (150 mL) and water (150 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 75 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a dark foam (4.32 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.90 (3H, d), 1.25 (3H, s), 3.45 (1H, d), 3.60 (1H, d), 6.55-6.70 (3H, m) and 7.15-7.25 (5H, m).
MS (Electrospray): M/Z (MH^+) 310.1; $C_{20}H_{27}N_3$ +H requires 310.2.

Preparation 17: *Trans*-(±)-2-(difluoromethyl)-5-(3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole

[0144] A solution of *trans*-(±)-2-(difluoromethyl)-5-(1-benzyl-3,4-dimethyl-4-piperidinyl)-1*H*-benzimidazole (Example 22, 2.99 g, 5.41 mmol) in ethanol (80 mL) was treated with 10% palladium on activated charcoal (100 mg) and hydrogenated at 50°C for 72 hours. The reaction mixture was allowed to cool and the catalyst remove by filtration through a bed of Celite®, which was washed well with ethanol. The solution was concentrated *in* vacuo to give a yellow foam (1.36 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.65 (3H, d), 1.45 (3H, s), 6.90 (1H, t), 7.35 (1H, d), 7.55 (1H, s) and 7.65 (1H, d).
MS (Electrospray): M/Z (MH^+) 280.1; $C_{15}H_{19}F_2N_3$ +H requires 280.2.

Preparation 18: *Trans*-(±)-2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol

[0145] To a stirred solution of *trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenol (Preparation 20, 2.88 g, 9.96 mmol) in acetonitrile (85 mL) at 0°C was added a solution of nitronium tetrafluoroborate (1.59 g, 12.0 mmol) in acetonitrile (15 mL). After 2 hours the reaction mixture was diluted with aqueous saturated sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product which was purified via silica gel chromatography eluting with methanol : dichloromethane : ammonium hydroxide (10:489:1) to give the title compound (1.07 g) as a yellow oil.
NMR δ_H(400 MHz, C_6D_6) (selected data from free base): 0.71 (d, 3H), 0.87 (t, 3H), 0.92 (s, 3H), 1.02 (m, 1H), 1.23-1.32 (m, 6H), 1.42 (m, 2H), 1.52 (m, 1H), 1.93 (m, 2H), 2.18 (m, 3H), 2.33 (m, 1H), 2.55 (m, 1H), 6.28 (dd, 1H), 6.78 (d, 1H) and 7.62 (d, 1H).
MS (APCI+): M/Z (MH^+) 335.3; $C_{19}H_{30}N_2O_3$ +H requires 335.2.

Preparation 19: *Trans*-(±)-2-amino-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol

[0146] To a solution of *trans*-(±)-2-nitro-5-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenol (Preparation 18, 644 mg, 1.93 mmol) in tetrahydrofuran (15 mL) was added platinum(IV) oxide (9 mg, 39 pmol) and the reaction mixture was shaken under 345 kPa of hydrogen gas for 10 hours. The reaction mixture was purged with nitrogen, filtered under nitrogen and the crude product was then (typically) employ d directly in the subsequent reaction. On s me occasions, th product was purified aft r concentration *in vacuo* via silica gel chromatography eluting with m thanol : dichloromethane : ammonium hydroxide (10:989:1) to give the title compound as an air-sensitive oil.

NMR $\delta_H(C_6D_6)$ (selected data): 0.86 (t, 3H), 0.97 (d, 3H), 1.24-1.32 (m, 9H), 1.45 (m, 3H), 1.81 (m, 1H), 2.16-2.41 (m, 5H), 2.53 (m, 1H), 2.78 (m, 1H), 6.42-6.46 (m, 2H) and 6.64 (dd, 1H).
MS (APCI+): M/Z (MH+) 305.3; $C_{19}H_{32}N_2O$ +H requir s 305.3.

Preparation 20: *Trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-ph nol

[0147] To a stirred solution of *trans*-(±)-3-(3,4-dimethyl-4-piperidinyl)phenol (J. A. Werner et al, J. *Org. Chem.*, 1996, **61**, 587; 2.0 g, 9.8 mmol) in *N,N*-dimethylformamide (50 mL) was added sodium bicarbonate (1.76 g, 20.95 mmol) and bromohexane (1.64 g, 9.9 mmol). The reaction mixture was heated under reflux for 3 hours and then cooled to room temperature. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (4 x 50 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. This was purified by silica (50 g) column chromatography eluting with ethyl acetate : hexane : 0.880 ammonia (30:70:1) to give the title compound as a light brown oil (2.68 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (d, 3H), 0.85 (t, 3H), 1.15-1.25 (m, 6H), 1.3 (s, 3H), 2.0 (m, 1H), 2.35 (m, 4H), 2.6 (m, 2H) and 6.55-7.2 (m, 4H).
MS (Thermospray): M/Z (MH+) 290.2; $C_{19}H_{31}NO$ +H requires 290.3.

Preparation 21: *Trans*-(±)-2-methyl-2-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl) phenoxy] propionamide

[0148] To a solution of *trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 20, 20 g, 69.2 mmol) in 1,4-dioxan (250 mL) under an atmosphere of nitrogen was added caesium carbonate (32.5 g, 100 mmol) carefully followed by sodium hydride (60% dispersion in mineral oil, 4 g, 100 mmol) in four portions over 30 min. The resultant mixture was stirred for 30 min then 2-bromo-2-methylpropionamide (16.6 g, 100 mmol) was added and the mixture was heated under reflux overnight. The reaction mixture was cooled, filtered and concentrated in *vacuo* to give the crude product which was purified by silica (600 g) column chromatography, eluting with a gradient of ethyl acetate : hexane : 0.880 ammonia (30:70:1 to 50:50:1), to give recovered starting phenol (5.9 g) followed by the title compound as a white solid (14.3 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.75 (d, 3H), 0.85 (m, 3H), 2.0 (m, 1H), 2.3 (m, 4H), 2.5 (m, 2H), 2.8 (m, 1H), 5.45 (br s, 1H), 6.65 (br s, 1H) and 6.75-7.2 (m, 4H).
MS (Thermospray): M/Z (MH+) 375.4; $C_{23}H_{38}N_2O_2$ + H requires 375.3.

Preparation 22: *Trans*-(±)-*N*-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-phenyl]-2-hydroxy-2-methylpropionamide

[0149] To a solution of *trans*-(±)-2-methyl-2-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenoxy]propionamide (Preparation 21, 13.13 g, 35 mmol) in *N*-methylpyrrolidinone (175 mL) under an atmosphere of nitrogen was added sodium hydride (60% dispersion in mineral oil, 4 g, 100 mmol) in four portions over 30 min. The resultant mixture was stirred for 30 min and then heated at 170°C overnight. The reaction mixture was cooled, carefully poured onto water (200 mL) and extracted with diethyl ether (3 x 150 mL). The combined extracts were washed with water (2 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as an orange oil (12.9 g) which was used without further purification.
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 0.9 (m, 3H), 2.0 (m, 1H), 2.3 (m, 4H), 2.5 (m, 2H), 2.8 (m, 1H), 7.05-7.55 (m, 4H) and 8.75 (br s, 1H).
MS (Thermospray): M/Z (MH+) 375.4; $C_{23}H_{38}N_2O_2$ +H requires 375.3.

Preparation 23: *Trans*-(±)-3-(1-hexyl-3,4-dimethyl-4-piperidinyl)-aniline

[0150] A solution of *trans*-(±)-*N*-[3-(1-hexyl-3,4-dimethyl-4-piperidinyl)phenyl]-2-hydroxy-2-methylpropionamide (Preparation 22, 12.9 g, 34.3 mmol) in 1,4-dioxan : 5 *N* HCl (1:1, 150 mL) was heated under reflux overnight. The reaction mixture was cooled, diluted with water (100 mL) and extracted with diethyl ether (3 x 200 mL). The pH of the aqueous layer was adjusted to 8-9 using 5 *N* NaOH and extracted with dichloromethane (5 x 200 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in *vacuo* to give the crude product which was purified by silica (200 g) column chromatography, eluting with ethyl acetate : hexane : 0.880 ammonia (40:60:1), to afford the title compound as a clear oil (8.8 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 0.9 (m, 3H), 1.95 (m, 1H), 2.35 (m, 4H), 2.55 (m, 2H), 2.8 (m, 1H), 3.6 (s, 2H) and 6.5-7.1 (m, 4H).
MS (Thermospray): M/Z (MH+) 289.5; $C_{19}H_{32}N_2$ + H requires 289.3.

Pr paration 24: *Trans*-(±)-3-(1-benzyl-3,4-dim thyl-4-piperidinyl)-ph nol

[0151] To a stirr d solution of *trans*-(±)-3-(3,4-dimethyl-4-piperidinyl)ph nol (J. A. Werner et al, *J. Org. Chem.*, 1996, **61**, 587; 2.08 g, 10.15 mmol) in *N,N*-dimethylformamide (50 mL) was added sodium bicarbonate (1.70 g, 20.3 mmol) and benzyl bromide (1.35 mL, 11.2 mmol). The reaction mixtur was h ated under reflux for 90 min. Th reaction mixture was then diluted with water (75 mL) and extracted with dichloromethane (100, 50 and th n 25 mL). The organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product. This was purified by silica (70 g) column chromatography, eluting with ethyl acetate : hexane : 0.880 ammonia (30:70:1) to give the title compound as a pale pink oil (2.66 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 1.2 (s, 3H), 2.9 (d, 1H), 3.5 (d, 1H), 3.6 (d, 1H), 6.6-6.9 (m, 3H), 7.1-7.4 (m, 6H).
MS (Thermospray): M/Z (MH^+) 296.4; $C_{20}H_{25}NO$ + H requires 296.2.

Preparation 25 : *Trans*-(±)-2-methyl-2-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl) phenoxy] propionamide

[0152] To a solution of *trans*-(±)-3-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenol (Preparation 24, 12.57 g, 42.6 mmol) in 1,4-dioxan (250 mL) under an atmosphere of nitrogen was added caesium carbonate (49.5 g, 152 mmol) carefully followed by anhydrous sodium hydride (4 g, 168 mmol) in four portions over 30 min. The resultant mixture was stirred for 1 hour then 2-bromo-2-methylpropionamide (20.5 g, 124 mmol) was added and the mixture was heated under reflux overnight, The reaction mixture was cooled, filtered and concentrated *in vacuo* to give the crude product which was purified by silica (600 g) column chromatography, eluting with a gradient of ethyl acetate : hexane : 0.880 ammonia (25:75:1 to 100:0:1) to give recovered starting phenol (1.44 g), followed by the title compound as a clear oil (12.8 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 1.35 (s, 3H), 1.95 (m, 1H), 2.35 (m, 2H), 2.55 (m, 2H), 2.8 (m, 1H), 3.5 (m, 2H), 5.4 (br s, 1H), 6.65 (br s, 1H), 6.75-7.4 (m, 9H).
MS (Thermospray): M/Z (MH^+) 381.2; $C_{24}H_{32}N_2O_2$ + H requires 381.2.

Preparation 26: *Trans*-(±)-*N*-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)-phenyl]-2-hydroxy-2-methylpropionamide

[0153] To a solution of *trans*-(±)-2-methyl-2-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)phenoxy]propionamide (Preparation 25, 12.77 g, 33.6 mmol) in *N,N*-dimethylformamide (330 mL) under an atmosphere of nitrogen was added anhydrous sodium hydride (1.65 g, 69 mmol) in four portions over 30 min. The resultant mixture was stirred for 1 hour and then heated under reflux overnight. The reaction mixture was cooled, carefully treated with water (200 mL) and stirred for 1 hour. It was then further diluted with water (300 mL) and extracted with diethyl ether (3 x 500 mL). The combined extracts were washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow foam (14.25 g) which was purified by silica (500 g) column chromatography eluting with a gradient of ethyl acetate : hexane : 0.880 ammonia (25:75:1 to 30:70:1 to 40:60:1) to give the title compound as a cream solid (10.16 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 1.35 (s, 3H), 1.55 (m, 6H), 2.0 (m, 1H), 2.1-2.9 (m, 6H), 3.4-3.65 (m, 2H), 7.0-7.55 (m, 9H), 8.65 (br s, 1H).
MS (Thermospray): M/Z (MH^+) 381.2; $C_{24}H_{32}N_2O_2$ + H requires 381.2.

Preparation 27: *Trans*-(±)-3-(1-benzyl-3,4-dimethyl-4-piperidinyl)-aniline

[0154] A solution of *trans*-(±)-*N*-[3-(1-benzyl-3,4-dimethyl-4-piperidinyl)-phenyl]-2-hydroxy-2-methylpropionamide (Preparation 26, 10.1 g, 26.5 mmol) in 1,4-dioxan : 5 *N* hydrochloric acid (1:1, 200 mL) was heated under reflux overnight. The reaction mixture was cooled and basified to pH 13 with 10 *N* sodium hydroxide solution. It was then diluted with water (300 mL) and extracted with diethyl ether (3 x 300 mL). The combined extracts were washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil which was purified by silica (400 g) column chromatography, eluting with ethyl acetate : hexane : ammonium hydroxide (25:75:1) to give the title compound as a golden oil (7.6 g).
NMR δ_H(300 MHz, $CDCl_3$) (selected data from free base): 0.8 (d, 3H), 1.3 (s, 3H), 1.55 (m, 1H), 1.95 (m, 1H), 2.25-2.6 (m, 4H), 2.85 (m, 1H), 3.4-3.7 (m, 2H), 6.45-7.4 (m, 9H).
MS (Thermospray): M/Z (MH^+) 295.3; $C_{20}H_{26}N_2$ + H requires 295.2.

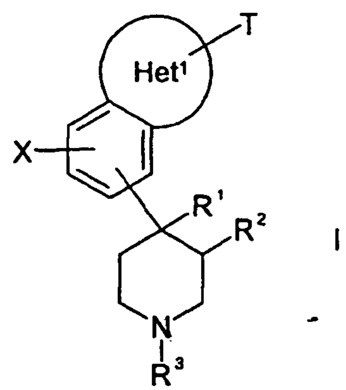
Biologi al A tivity

[0155] Th Ki values of certain compounds of th present invention in the opioid receptor binding assays w re d -

t rmined, and the compounds of Examples 3, 7, 12, 18, 21 and 28 were all found to hav Ki values f 4000 nM or less for the μ recept r. The compounds of the inv ntion also possess affinity at the δ and κ opioid receptors.

Claims

1. A compound of formula I,



I

wherein Het^1 represents a 5-, 6- or 7-membered heterocyclic ring containing at least one nitrogen atom, and optionally one or more heteroatoms selected from oxygen or sulfur, and which heterocyclic ring is fully saturated, partially unsaturated or aromatic in character;
T represents one or more optional substituents selected from H, halo, OH, =O, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which latter three groups are optionally substituted by one or more halo atoms), aryl(C_{1-6})alkyl (the aryl part of which is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), -N(R^{4a})(R^5), -N(R^{4b})S(O)$_m$$R^6$, -N($R^{4c}$)C(O)$R^{7a}$ and -N(R^{4d})C(O)OR^{7b}, provided that when Het^1 contains less than three C-atoms (i.e. where the only two C-atoms are those provided by the fused benzene ring) and at least one heteroatom selected from oxygen and sulfur, then T does not represent halo or C_{1-6} alkoxy (which latter group is optionally substituted by one or more halo atoms);
R^{4a} to R^{4d} and R^5 independently represent H, C_{1-6} alkyl (which latter group is optionally substituted by one or more halo atoms), or R^{4a} and R^5, together with the nitrogen atom to which they are attached, form a 4- to 6-membered heterocyclic ring (which ring is optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo);
R^6 represents C_{1-6} alkyl or aryl, which two groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or nitro;
R^{7a} and R^{7b} independently represent C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, aryl (which four groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or nitro), or R^{7a} represents H;
m is 0, 1 or 2;
R^1 and R^2 are each independently H or C_{1-4} alkyl;
R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and -N(R^{8a})(R^{8b})), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{8c}, S(O)$_n$$R^{8d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, N(R^{9a})S(O)$_2$$R^{10}$, Het^2, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A^1-N(R^{9b})(R^{9c});
n is 0, 1 or 2;
W repr sents a single bond, C(O) or S(O)$_p$;
A^1 represents a single bond r C_{1-10} alkylene;
provided that when both W and A^1 represent single bonds, then the group -N(R^{9b})(R^{9c}) is not directly attached to an unsaturated carbon atom;

p is 0, 1 or 2;
R^{8a} to R^{8d} each independ ntly repres nt H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substitut d by or one or more substitu nts selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or mor halo atoms)) or Het^3;
provided that R^{8d} does not represent H when n r presents 1 or 2;
R^{9a} to R^{9c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^4, or R^{9b} and R^{9c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O, S and/or an $N(R^{11})$ group and is optionally substituted by one or more C_{1-4} alkyl groups;
R^{10} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, nitro, amino or halo;
R^{11} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, A^2-(C_{3-8} cycloalkyl) or A^2-aryl;
A^2 represents C_{1-6} alkylene;
Het^2, Het^3 and Het^4 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);
X represents one or two optional substituents on the benzene ring, which substituents are selected from halo, C_{1-4} alkyl, C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);
or pharmaceutically, or veterinarily, acceptable derivatives thereof.

2. A compound as claimed in Claim 1, wherein Het^1 is fused at the 3,4-position on the benzene ring relative to the piperidine ring.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^1 represents C_{1-2} alkyl.

4. A compound as claimed in any one of Claims 1 to 3, wherein R^2 represents H or C_{1-2} alkyl.

5. A compound as claimed in any one of Claims 1 to 4, wherein R^3 represents saturated C_{1-10} alkyl, optionally interrupted by oxygen and/or optionally substituted by one or more substituents selected from OR^{8c}, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{9a})S(O)_2R^{10}$, Het^2, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN, CH_2CN, $CONH_2$ and CF_3), and/or $-W-A^1-N(R^{9b})(R^{9c})$.

6. A compound as claimed in any one of Claims 1 to 5, wherein R^{8c} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl or C_{1-4} alkylphenyl (which latter two groups are optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN, CH_2CN, $CONH_2$ and CF_3); R^{9a} to R^{9c} each independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter two groups are optionally substituted by or one or more substituents selected from C_{1-2} alkyl, C_{1-2} alkoxy, OH or halo); R^{10} represents C_{1-4} alkyl or aryl (which two groups are optionally substituted by or one or more substituents selected from C_{1-2} alkyl, C_{1-2} alkoxy, nitro or halo); W represents C(O) or $S(O)_2$; and/or A^1 represents a single bond or C_{1-4} alkylene.

7. A compound as claimed in any one of Claims 1 to 6, wherein T represents H, OH, C_{1-6} alkyl (optionally substituted with one or more halo atoms), C_{1-4} alkoxy, C_{4-6} cycloalkyl, aryl(C_{1-3})alkyl, $-NH(R^5)$ or $-N(H)S(O)_2R^6$.

8. A compound as claimed in any one of Claims 1 to 7, wherein R^5 represents H or C_{1-2} alkyl; and/or R^6 represents C_{1-2} alkyl.

9. A compound as claimed in any one of Claims 1 to 8, wherein Het^1 represents a 5- or 6-membered heterocyclic ring containing an NH group.

10. A compound as claimed in any one of Claims 1 to 9, wher in R^1 and R^2 both repr s nt methyl groups in the mutually *trans* configuration.

11. A compound as claimed in any one of Claims 1 to 10, wherein R^3 represents saturated C_{1-7} alkyl, optionally substitut d by one or m re substituents selected from CN, halo, O-(C_{1-4} alkyl), O-(phenyl), O-(C_{1-4} alkylph nyl) and ph nyl (which latter thre groups are optionally substituted by one or more C_{1-4} alkyl groups).

12. A compound as claimed in any one of Claims 1 to 11, wherein T represents H, NH_2, C_{4-6} cycloalkyl or C_{1-6} alkyl (which latter group is optionally substituted by one or more halo atoms).

13. A compound as claimed in any one of Claims 1 to 8 or 10 to 12, wherein Het[1], together with the benzene ring to which it is fused, represents an aromatic heterocycle selected from benzimidazole, benzotriazole, benzoxadiazole, benzoxazole, benzothiazole, cinnoline, indole, isoquinoline, phthalazine, quinazoline, quinoline or quinoxaline.

14. A compounds as claimed in any one of Claims 1 to 13, wherein T represents H, CH_3, CHF_2, CF_3, ethyl, isopropyl, C_{4-5} cycloalkyl or NH_2.

15. A compound as claimed in any one of Claims 1 to 14, wherein R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from O-(C_{2-4} alkyl), O-(phenyl), O-(C_{1-2} alkylphenyl) and phenyl (which latter group is optionally substituted by one or more C_{1-2} alkyl groups).

16. A compound as claimed in any one of Claims 1 to 15, wherein Het[1], together with the benzene ring to which it is fused, represents a benzimidazole group.

17. A compound as defined in any one of Claims 1 to 16, for use as a medicament.

18. A compound as defined in any one of Claims 1 to 16, for use as an animal medicament.

19. A formulation comprising a compound as defined in any one of Claims 1 to 16, in admixture with a pharmaceutically, or a veterinarily, acceptable adjuvant, diluent or carrier.

20. A formulation as claimed in Claim 19, which is a veterinary formulation.

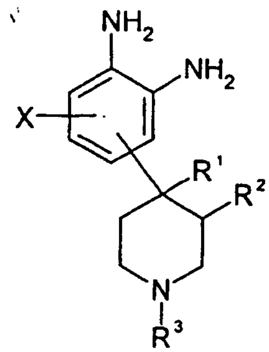
21. The use of a compound as defined in any one of Claims 1 to 16, in the manufacture of a medicament for the curative or prophylactic treatment of a disease mediated via an opiate receptor.

22. The use as claimed in Claim 21, wherein the disease is pruritus.

23. A method of treating or preventing a disease mediated by an opiate receptor, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 16, to a patient in need of such treatment.

24. A process for the preparation of a compound as defined in Claim 1, which comprises:

a) for compounds of formula I wherein Het[1] represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which three groups are optionally substituted by one or more halo atoms) or aryl(C_{1-6})alkyl (the aryl part of which is optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy, which latter two groups are optionally substituted by one or more halo atoms), reaction of a corresponding compound of formula II,



II

wherein R^1, R^2, R^3 and X are as defined in Claim 1, with a compound of formula III,

$$T^a\text{-}C(OR^{12})_3 \qquad \text{III,}$$

wherein T^a represents H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl (which latter three groups are optionally substituted by one or more halo atoms) or aryl(C_{1-6})alkyl (the aryl group of which is optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy, which latter two groups are optionally substituted by one or more halo atoms) and R^{12} represents C_{1-2} alkyl;

b) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by T^a, wherein T^a is as defined above provided that it does not represent C_{1-6} alkoxy or C_{1-6} haloalkoxy, reaction of a corresponding compound of formula II, as defined above, with a compound of formula XII,

$$T^a\text{-}C(O)OH \qquad \text{XII}$$

or a suitable derivative thereof, wherein T^a is as defined above provided that it does not represent C_{1-6} alkoxy or C_{1-6} haloalkoxy;

c) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, optionally substituted in the 2-position by a hydroxy group, reaction of a corresponding compound of formula II, as defined above, with a suitable derivative of carbonic acid;

d) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, substituted in the 2-position by a $N(H)S(O)_2R^6$ group, wherein R^6 is as defined in Claim 1, reaction of a corresponding compound of formula II, as defined above, with a compound of formula XIII,

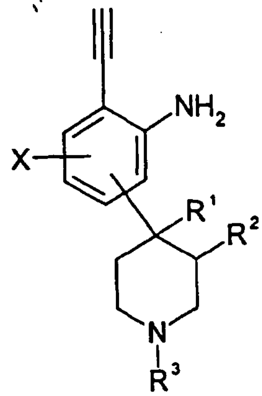
$$(L^2)_2C{=}NS(O)_2R^6 \qquad \text{XIII}$$

wherein L^2 represents a leaving group and R^6 is as defined in Claim 1;

e) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzimidazole, substituted in the 2-position by an amino group, hydrolysis of a corresponding compound of formula I in which Het^1 represents the 5-membered ring of a benzimidazole substituted in the 2-position by a $N(H)S(O)_2R^6$ group, wherein R^6 is as defined in Claim 1;

f) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzotriazole, reaction of a corresponding compound of formula II, as defined above, with a source of the nitrosonium cation;

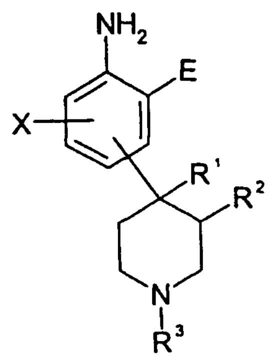
g) for compounds of formula I wherein Het^1 represents the 5-membered ring of an indole, cyclisation of a corresponding compound of formula XIV,



XIV

wherein R^1, R^2, R^3 and X are as defined in Claim 1;

h) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzoxazole or benzothiazole, optionally substituted in the 2-position by T^a, wherein T^a is as defined above, reaction of a corresponding compound of formula XVI,

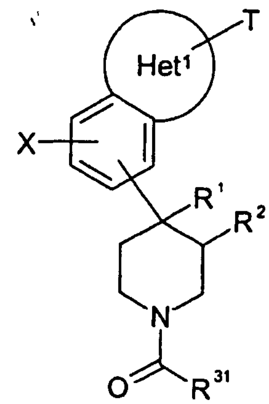


XVI

wherein E represents OH or SH, and R^1, R^2, R^3 and X are as defined in Claim 1, with a compound of formula III or a compound of formula XII, as defined above;

i) for compounds of formula I wherein Het^1 represents the 5-membered ring of a benzoxazole or benzothiazole, optionally substituted in the 2-position with an OH group, reaction of a corresponding compound of formula XVI, as defined above, with a derivative of carbonic acid;

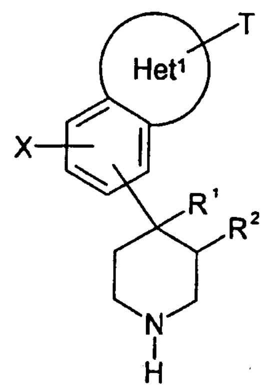
j) for compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^2, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified in Claim 1 in respect to R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^2 is as defined in Claim 1, reduction of a corresponding compound of formula XIX,



XIX

wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^2, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9}) alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{8c}, $S(O)_nR^{8d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{9a})S(O)_2R^{10}$, Het^2, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{9b})(R^{9c})$, and R^1, R^2, R^{8c}, R^{8d}, R^{9a} to R^{9c}, R^{10}, Het^1, Het^2, n, W, A^1, T and X are as defined in Claim 1;

k) reaction of a corresponding compound of formula XX,



XX

wherein Het^1, R^1, R^2, T and X are as defined in Claim 1, with a compound of formula XI,

$$R^3L^1 \qquad \text{XI}$$

wherein L^1 is a leaving group and R^3 is as defined in Claim 1;

l) for compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined in Claim 1, is instead optionally substituted by R^{31}, wherein R^{31} is as defined above, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXII,

$$R^{31}CHO \qquad \text{XXII}$$

wherein R^{31} is as defined above;
m) for compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturat d from 1- to 3-C (relativ to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{8d}$, $S(O)_2R^{8d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{9b})(R^{9c})$, $-S(O)-A^1-N(R^{9b})(R^{9c})$, or $-S(O)_2-A^1-N(R^{9b})(R^{9c})$, wherein R^{8d}, R^{9b}, R^{9c} and A^1 are as defined in Claim 1, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXIII,

$$R^{3a}\text{-}Z \qquad \text{XXIII}$$

wherein R^{3a} represents R^3 as defined in Claim 1 except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{8d}$, $S(O)_2R^{8d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{9b})(R^{9c})$, $-S(O)-A^1-N(R^{9b})(R^{9c})$, or $-S(O)_2-A^1-N(R^{9b})(R^{9c})$, wherein R^{8d}, R^{9b}, R^{9c} and A^1 are as defined in Claim 1;
n) conversion of one functional group on an alkyl, heterocyclic or aryl group in a compound of formula I to another.

25. A compound of formula II, as defined in Claim 24, or a protected derivative thereof.

26. A compound of formula XIV, as defined in Claim 24, or a protected derivative thereof.

27. A compound of formula XVI, as defined in Claim 24, or a protected derivative thereof.

28. A compound of formula XIX, as defined in Claim 24, or a protected derivative thereof.

29. A compound of formula XX, as defined in Claim 24, or a protected derivative thereof.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number
EP 00 30 4227

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 4 737 505 A (GUILLAUME JACQUES ET AL) 12 April 1988 (1988-04-12) * example 23 * * column 6, paragraphs 4-6 * ---	1,17-23	C07D211/26 C07D401/04 C07D413/04 A61K31/454 A61P17/04
X	WO 98 50358 A (GASTER LARAMIE MARY ;RAMI HARSHAD KANTILAL (GB); WYMAN PAUL ADRIAN) 12 November 1998 (1998-11-12) * page 29; examples 38,39 * ---	1,17,19	
P,X	WO 99 67237 A (KROG JENSEN CHRISTIAN ;MIKKELSEN IVAN (DK); LUNDBECK & CO AS H (DK) 29 December 1999 (1999-12-29) * page 13, line 22 * * example 5A * ---	1,17,19	
X	WO 96 03400 A (PFIZER ;MACOR JOHN EUGENE (US)) 8 February 1996 (1996-02-08) * example 9 * --- -/--	1,17,19	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D A61K A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 23 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 September 2000	Seitner, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 30 4227

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 179 (C-590), 26 April 1989 (1989-04-26) & JP 01 006269 A (YOSHITOMI PHARMACEUT IND LTD), 10 January 1989 (1989-01-10) * abstract *	1,17,19	
D,A	EP 0 506 468 A (LILLY CO ELI) 30 September 1992 (1992-09-30) * example 6 *	1,17-23	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C16)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 30 4227

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-09-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4737505 A	12-04-1988	FR 2567884 A	24-01-1986
		DE 3572977 D	19-10-1989
		EP 0169148 A	22-01-1986
		JP 6057706 B	03-08-1994
		JP 61037780 A	22-02-1986
WO 9850358 A	12-11-1998	AU 7431098 A	27-11-1998
		CN 1260781 T	19-07-2000
		EP 0975593 A	02-02-2000
		NO 995065 A	15-10-1999
		PL 336317 A	19-06-2000
WO 9967237 A	29-12-1999	AU 4359299 A	10-01-2000
WO 9603400 A	08-02-1996	CA 2194984 A	08-02-1996
		EP 0773942 A	21-05-1997
		FI 970310 A	24-01-1997
		JP 9508137 T	19-08-1997
JP 01006269 A	10-01-1989	NONE	
EP 0506468 A	30-09-1992	US 5159081 A	27-10-1992
		CA 2064382 A	30-09-1992
		DE 69202186 D	01-06-1995
		DE 69202186 T	05-10-1995
		ES 2072096 T	01-07-1995
		JP 3059292 B	04-07-2000
		JP 5097807 A	20-04-1993
		US 5270328 A	14-12-1993

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82